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<b>(54) Title:</b> A METHOD OF DESIGNING ALPHA-AMYLASE MUTANTS WITH PREDETERMINED PROPERTIES		
<b>(57) Abstract</b> <p>A method of constructing a variant of a parent Termamyl-like <math>\alpha</math>-amylase, which variant has <math>\alpha</math>-amylase activity and at least one altered property as compared to the parent <math>\alpha</math>-amylase, comprises i) analysing the structure of the parent Termamyl-like <math>\alpha</math>-amylase to identify at least one amino acid residue or at least one structural part of the Termamyl-like <math>\alpha</math>-amylase structure, which amino acid residue or structural part is believed to be of relevance for altering the property of the parent Termamyl-like <math>\alpha</math>-amylase (as evaluated on the basis of structural or functional considerations), ii) constructing a Termamyl-like <math>\alpha</math>-amylase variant, which as compared to the parent Termamyl-like <math>\alpha</math>-amylase, has been modified in the amino acid residue or structural part identified in i) so as to alter the property, and iii) testing the resulting Termamyl-like <math>\alpha</math>-amylase variant for the property in question.</p>		

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## A METHOD OF DESIGNING ALPHA-AMYLASE MUTANTS WITH PREDETERMINED PROPERTIES

## FIELD OF THE INVENTION

- 5 The present invention relates to a novel method of designing  $\alpha$ -amylase mutants with predetermined properties, which method is based on the hitherto unknown three-dimensional structure of bacterial  $\alpha$ -amylases.

## 10 BACKGROUND OF THE INVENTION

$\alpha$ -Amylases ( $\alpha$ -1,4 glucan-4-glucanohydrolase, EC 3.2.1.1) constitute a group of enzymes which is capable of hydrolyzing starch and other linear and branched 1,4-glucosidic oligo- and  
15 polysaccharides. Almost all  $\alpha$ -amylases studied have a few conserved regions with approximately the same length and spacing. One of these regions resembles the  $\text{Ca}^{2+}$  binding site of calmodulin and the others are thought to be necessary for the active centre and/or binding of the substrate.

20 While the amino acid sequence and thus primary structure of a large number of  $\alpha$ -amylases are known, it has proved very difficult to determine the three-dimensional structure of all  $\alpha$ -amylases. The three-dimensional structure can be determined  
25 by X-ray crystallographic analysis of  $\alpha$ -amylase crystals, but it has proven difficult to obtain  $\alpha$ -amylase crystals suitable for actually solving the structure.

Until now the three-dimensional structure of only a few  
30  $\alpha$ -amylases have been determined at high resolution. These include the structure of the *Aspergillus oryzae* TAKA  $\alpha$ -amylase (Swift et al., 1991), the *Aspergillus niger* acid amylase (Brady et al, 1991), the structure of pig pancreatic  $\alpha$ -amylase (Qian et al., 1993), and the barley alpha-amylase (Kadziola et al.  
35 1994, Journal of Molecular Biology 239: 104-121, A.Kadziola, Thesis, Dept of Chemistry, U. of Copenhagen, Denmark). Furthermore, the three-dimensional structure of a *Bacillus circulans* cyclodextrin glycosyltransferase (CGTase) is known

(Klein et al., 1992) (Lawson et al., 1994). The CGTase catalyzes the same type of reactions as  $\alpha$ -amylases and exhibits some structural resemblance with  $\alpha$ -amylases.

5 Furthermore, crystallization and preliminary X-ray studies of *B. subtilis*  $\alpha$ -amylases have been described (Chang et al. (1992) and Mizuno et al. (1993)). No final *B. subtilis* structure has been reported. Analogously, the preparation of *B. licheniformis*  $\alpha$ -amylase crystals has been reported (Suzuki et al. (1990)), but  
10 no subsequent report on X-ray crystallographic analysis or three-dimensional structure are available.

Several research teams have attempted to build three-dimensional structures on the basis of the above known  
15  $\alpha$ -amylase structures. For instance, Vihinen et al. (J. Biochem. 107, 267-272, 1990), disclose the modelling (or computer simulation) of a three-dimensional structure of the *Bacillus stearothermophilus*  $\alpha$ -amylase on the basis of the TAKA amylase structure. The model was used to investigate hypothetical  
20 structural consequences of various site-directed mutations of the *B. stearothermophilus*  $\alpha$ -amylase. E.A. MacGregor (1987) predicts the presence of  $\alpha$ -helices and  $\beta$ -barrels in  $\alpha$ -amylases from different sources, including barley, pig pancreas and *Bacillus amyloliquefaciens* on the basis of the known structure  
25 of the *A. oryzae* TAKA  $\alpha$ -amylase and secondary structure predicting algorithms. Furthermore, the possible loops and subsites which may be found to be present in, e.g., the *B. amyloliquefaciens*  $\alpha$ -amylase are predicted (based on a comparison with the *A. oryzae* sequence and structure).

30 A.E. MacGregor (Starch/Stärke 45 (1993), No. 7, p. 232-237) presents a review of the relationship between the structure and activity of  $\alpha$ -amylase related enzymes.

35 Hitherto, no three-dimensional structure has been available for the industrially important *Bacillus*  $\alpha$ -amylases (which in the present context are termed "Termamyl-like  $\alpha$ -amylases"),

including the *B. licheniformis*, the *B. amyloliquefaciens*, and the *B. stearothermophilus*  $\alpha$ -amylase.

#### BRIEF DISCLOSURE OF THE INVENTION

- 5 The three-dimensional structure of a Termamyl-like bacterial  $\alpha$ -amylase has now been elucidated. On the basis of an analysis of said structure it is possible to identify structural parts or specific amino acid residues which from structural or
- 10 functional considerations appear to be important for conferring the various properties to the Termamyl-like  $\alpha$ -amylases. Furthermore, when comparing the Termamyl-like  $\alpha$ -amylase structure with known structures of the fungal and mammalian  $\alpha$ -amylases mentioned above, it has been found that some
- 15 similarities exist between the structures, but also that some striking, and not previously predicted structural differences between the  $\alpha$ -amylases exist. The present invention is based on these findings.
- 20 Accordingly, in a first aspect the invention relates to a method of constructing a variant of a parent Termamyl-like  $\alpha$ -amylase, which variant has  $\alpha$ -amylase activity and at least one altered property as compared to said parent  $\alpha$ -amylase, which method comprises
- 25
- i) analysing the structure of the Termamyl-like  $\alpha$ -amylase with a view to identifying at least one amino acid residue or at least one structural part of the Termamyl-like  $\alpha$ -amylase structure, which amino acid residue or structural part is
  - 30 believed to be of relevance for altering said property of the parent Termamyl-like  $\alpha$ -amylase (as evaluated on the basis of structural or functional considerations),
  - ii) constructing a Termamyl-like  $\alpha$ -amylase variant, which as
  - 35 compared to the parent Termamyl-like  $\alpha$ -amylase, has been modified in the amino acid residue or structural part identified in i) so as to alter said property, and

iii) testing the resulting Termamyl-like  $\alpha$ -amylase variant for said property.

5 In a second aspect the present invention relates to a method of constructing a variant of a parent Termamyl-like  $\alpha$ -amylase, which variant has  $\alpha$ -amylase activity and one or more altered properties as compared to said parent  $\alpha$ -amylase, which method comprises

10 i) comparing the three-dimensional structure of the Termamyl-like  $\alpha$ -amylase with the structure of a non-Termamyl-like  $\alpha$ -amylase,

ii) identifying a part of the Termamyl-like  $\alpha$ -amylase structure which is different from the non-Termamyl-like  $\alpha$ -amylase  
15 structure, and

iii) modifying the part of the Termamyl-like  $\alpha$ -amylase identified in ii) whereby a Termamyl-like  $\alpha$ -amylase variant is obtained, one or more properties of which differ from the parent Termamyl-like  $\alpha$ -amylase.

20

In a third aspect the invention relates to a method of constructing a variant of a parent non-Termamyl-like  $\alpha$ -amylase, which variant has  $\alpha$ -amylase activity and one or more altered properties as compared to said parent  $\alpha$ -amylase, which method  
25 comprises

i) comparing the three-dimensional structure of the non-Termamyl-like  $\alpha$ -amylase with the structure of a Termamyl-like  $\alpha$ -amylase,

ii) identifying a part of the non-Termamyl-like  $\alpha$ -amylase  
30 structure which is different from the Termamyl-like  $\alpha$ -amylase structure, and

iii) modifying the part of the non-Termamyl-like  $\alpha$ -amylase identified in ii) whereby a non-Termamyl-like  $\alpha$ -amylase variant is obtained, one or more properties of which differ from the  
35 parent Termamyl-like  $\alpha$ -amylase.

The property which may be altered by the above methods of the present invention may, e.g., be substrate specificity,

substrate binding, substrate cleavage pattern, temperature stability, pH dependent activity, pH dependent stability (especially increased stability at low (e.g. pH<6, in particular pH<5) or high (e.g. pH>9) pH values), stability  
5 towards oxidation, Ca<sup>2+</sup>-dependency, specific activity, and other properties of interest. For instance, the alteration may result in a variant which, as compared to the parent Termamyl-like  $\alpha$ -amylase, has an increased specific activity at a given pH and/or an altered substrate specificity.

10

In still further aspects the invention relates to variants of a Termamyl-like  $\alpha$ -amylase, DNA encoding such variants and methods of preparing the variants. Finally, the invention relates to the use of the variants for various industrial  
15 purposes.

#### DETAILED DISCLOSURE OF THE INVENTION

##### The Termamyl-like $\alpha$ -amylase

20

It is well known that a number of alpha-amylases produced by *Bacillus* spp. are highly homologous on the amino acid level. For instance, the *B. licheniformis*  $\alpha$ -amylase comprising the amino acid sequence shown in SEQ ID No. 2 (commercially  
25 available as Termamyl®) has been found to be about 89% homologous with the *B. amyloliquefaciens*  $\alpha$ -amylase comprising the amino acid sequence shown in SEQ ID No. 4 and about 79% homologous with the *B. stearothermophilus*  $\alpha$ -amylase comprising the amino acid sequence shown in SEQ ID No. 6. Further  
30 homologous  $\alpha$ -amylases include an  $\alpha$ -amylase derived from a strain of the *Bacillus* sp. NCIB 12289, NCIB 12512, NCIB 12513 or DSM 9375, all of which are described in detail in WO 95/26397, and the  $\alpha$ -amylase described by Tsukamoto et al., 1988, Biochemical and Biophysical Research Communications, Vol.  
35 151, No. 1. Still other homologous  $\alpha$ -amylases include the  $\alpha$ -amylase produced by the *B. licheniformis* described in EP 252 666 (ATCC 27811), and the  $\alpha$ -amylases identified in WO 91/00353 and WO 94/18314. Other commercial Termamyl-like E.

*licheniformis*  $\alpha$ -amylases are Optitherm® and Takatherm® (available from Solvay), Maxamyl® (available from Gist-brocades/Genencor), Spezym AA® (available from Genencor), and Keistase® (available from Daiwa).

5

Because of the substantial homology found between these  $\alpha$ -amylases, they are considered to belong to the same class of  $\alpha$ -amylases, namely the class of "Termamyl-like  $\alpha$ -amylases".

10 Accordingly, in the present context, the term "Termamyl-like  $\alpha$ -amylase" is intended to indicate an  $\alpha$ -amylase which, on the amino acid level, exhibits a substantial homology to Termamyl®, i.e. the *B. licheniformis*  $\alpha$ -amylase SEQ ID NO 2. In other words, a Termamyl-like  $\alpha$ -amylase is an  $\alpha$ -amylase, which has the  
15 amino acid sequence shown in SEQ ID No. 2, 4 or 6 herein, or the amino acid sequence shown in SEQ ID NO 1 or 2 of WO 95/26397 or in Tsukamoto et al., 1988, or i) which displays at least 60%, such as at least 70%, e.g. at least 75%, or at least 80%, e.g. at least 85%, at least 90% or at least 95% homology  
20 with at least one of said amino acid sequences and/or ii) displays immunological cross-reactivity with an antibody raised against at least one of said  $\alpha$ -amylases, and/or iii) is encoded by a DNA sequence which hybridizes to the DNA sequences encoding the above specified  $\alpha$ -amylases which are apparent from  
25 SEQ ID Nos. 1, 3 and 5 of the present application, and SEQ ID NO 4 and 5 of WO 95/26397, respectively.

In connection with property i) the "homology" may be determined by use of any conventional algorithm, preferably by use of the  
30 GAP programme from the GCG package version 7.3 (June 1993) using default values for GAP penalties (Genetic Computer Group (1991) Programme Manual for the GCG Package, version 7, 575 Science Drive, Madison, Wisconsin, USA 53711).

35 Property ii) of the  $\alpha$ -amylase, i.e. the immunological cross reactivity, may be assayed using an antibody raised against or reactive with at least one epitope of the relevant Termamyl-like  $\alpha$ -amylase. The antibody, which may either be monoclonal or

- polyclonal, may be produced by methods known in the art, e.g. as described by Hudson et al., 1989. The immunological cross-reactivity may be determined using assays known in the art, examples of which are Western Blotting or radial immunodiffusion assay, e.g. as described by Hudson et al., 1989. In this respect, immunological cross-reactivity between the  $\alpha$ -amylases having the amino acid sequences SEQ ID Nos. 2, 4 and 6, respectively, has been found.
- 10 The oligonucleotide probe used in the characterization of the Termamyl-like  $\alpha$ -amylase in accordance with property iii) above may suitably be prepared on the basis of the full or partial nucleotide or amino acid sequence of the  $\alpha$ -amylase in question. Suitable conditions for testing hybridization involve
- 15 presoaking in 5xSSC and prehybridizing for 1h at  $-40^{\circ}\text{C}$  in a solution of 20% formamide, 5xDenhardt's solution, 50mM sodium phosphate, pH 6.8, and 50 $\mu\text{g}$  of denatured sonicated calf thymus DNA, followed by hybridization in the same solution supplemented with 100 $\mu\text{M}$  ATP for 18h at  $-40^{\circ}\text{C}$ , or other methods
- 20 described by e.g. Sambrook et al., 1989.

In the present context, "derived from" is intended not only to indicate an  $\alpha$ -amylase produced or producible by a strain of the organism in question, but also an  $\alpha$ -amylase encoded by a DNA

25 sequence isolated from such strain and produced in a host organism transformed with said DNA sequence. Finally, the term is intended to indicate an  $\alpha$ -amylase which is encoded by a DNA sequence of synthetic and/or cDNA origin and which has the identifying characteristics of the  $\alpha$ -amylase in question. The

30 term is also intended to indicate that the parent  $\alpha$ -amylase may be a variant of a naturally occurring  $\alpha$ -amylase, i.e. a variant which is the result of a modification (insertion, substitution, deletion) of one or more amino acid residues of the naturally occurring  $\alpha$ -amylase.

35

Parent hybrid  $\alpha$ -amylases

The parent  $\alpha$ -amylase (being a Termamyl-like or non-Termamyl-like  $\alpha$ -amylase) may be a hybrid  $\alpha$ -amylase, i.e. an  $\alpha$ -amylase  
5 which comprises a combination of partial amino acid sequences derived from at least two  $\alpha$ -amylases.

The parent hybrid  $\alpha$ -amylase may be one which on the basis of amino acid homology and/or immunological cross-reactivity  
10 and/or DNA hybridization (as defined above) can be determined to belong to the Termamyl-like  $\alpha$ -amylase family. In this case, the hybrid  $\alpha$ -amylase is typically composed of at least one part of a Termamyl-like  $\alpha$ -amylase and part(s) of one or more other  $\alpha$ -amylases selected from Termamyl-like  $\alpha$ -amylases or non-  
15 Termamyl-like  $\alpha$ -amylases of microbial (bacterial or fungal) and/or mammalian origin.

Thus, the parent hybrid  $\alpha$ -amylase may comprise a combination of at least two Termamyl-like  $\alpha$ -amylases, or of at least one  
20 Termamyl-like and at least one non-Termamyl-like bacterial  $\alpha$ -amylase, or of at least one Termamyl-like and at least one fungal  $\alpha$ -amylase. For instance, the parent  $\alpha$ -amylase comprises a C-terminal part of an  $\alpha$ -amylase derived from a strain of *B. licheniformis* and a N-terminal part of an  $\alpha$ -amylase derived  
25 from a strain of *B. amyloliquefaciens* or from a strain of *B. stearothermophilus*. For instance, the parent  $\alpha$ -amylase comprises at least 430 amino acid residues of the C-terminal part of the *B. licheniformis*  $\alpha$ -amylase, and may, e.g. comprise  
a) an amino acid segment corresponding to the 37 N-terminal  
30 amino acid residues of the *B. amyloliquefaciens*  $\alpha$ -amylase having the amino acid sequence shown in SEQ ID No. 4 and an amino acid segment corresponding to the 445 C-terminal amino acid residues of the *B. licheniformis*  $\alpha$ -amylase having the amino acid sequence shown in SEQ ID No. 2, or b) an amino acid  
35 segment corresponding to the 68 N-terminal amino acid residues of the *B. stearothermophilus*  $\alpha$ -amylase having the amino acid sequence shown in SEQ ID No. 6 and an amino acid segment corresponding to the 415 C-terminal amino acid residues of the

*B. licheniformis*  $\alpha$ -amylase having the amino acid sequence shown in SEQ ID No. 2.

Analogously, the parent hybrid  $\alpha$ -amylase may belong to a non-Termamyl-like  $\alpha$ -amylase family, e.g. the Fungamyl-like  $\alpha$ -amylase family. In that case the hybrid may comprise at least one part of an  $\alpha$ -amylase belonging to the non-Termamyl-like  $\alpha$ -amylase family in combination with one or more parts derived from other  $\alpha$ -amylases.

10

The three-dimensional Termamyl-like  $\alpha$ -amylase structure

The Termamyl-like  $\alpha$ -amylase which was used to elucidate the three-dimensional structure forming the basis for the present invention consists of the 300 N-terminal amino acids of the *B. amyloliquefaciens*  $\alpha$ -amylase (with the amino acid sequence shown in SEQ ID No. 4) and amino acids 301-483 of the C-terminal end of the *B. licheniformis*  $\alpha$ -amylase with the amino acid sequence SEQ ID No. 2. The bacterial  $\alpha$ -amylase belongs to the "Termamyl-like  $\alpha$ -amylase family" and the present structure is believed to be representative for the structure of any Termamyl-like  $\alpha$ -amylase.

The structure of the  $\alpha$ -amylase was solved in accordance with the principle for X-ray crystallographic methods given in "X-Ray Structure Determination", Stout, G.K. and Jensen, L.H., John Wiley & Sons, inc. NY, 1989. The structural coordinates for the solved crystal structure of the  $\alpha$ -amylase at 2.2 Å resolution using the isomorphous replacement method are given in a standard PDB format (Brookhaven Protein Data Base) in Appendix 1. It is to be understood that Appendix 1 forms part of the present application.

Amino acid residues of the enzyme are identified by three-letter amino acid code (capitalized letters).

The  $\alpha$ -amylase structure is made up of three globular domains ordered A, B, and C with respect to sequence, which lie

approximately along a line in the order B, A, C. The domains can be defined as being residues 1-103 and 206-395 for domain A, residues 104-205 for domain B, and residues 396-483 for domain C, the numbers referring to the *B. licheniformis*  $\alpha$ -amylase. This gives rise to an elongated molecule, the longest axis being about 85Å. The widest point perpendicular to this axis is approximately 50Å and spans the central A domain. The active site residues of the *B. licheniformis*  $\alpha$ -amylase (SEQ ID NO 2) are D323, D231 and E261.

10

#### Domain A

Domain A is the largest domain and contains the active site (comprised of a cluster of three amino acid residues placed at the bottom of a deep cleft in the enzyme's surface). Domain A of all known  $\alpha$ -amylase structures have the same overall fold, viz. the (beta/alpha)<sub>8</sub> barrel with 8 central beta strands (number 1-8) and 8 flanking  $\alpha$ -helices. The  $\beta$ -barrel is defined by McGregor *op. cit.* The C-terminal end of Beta strand 1 is connected to helix 1 by a loop denoted loop 1 and an identical pattern is found for the other loops. These loops show some variation in size and some can be quite extensive.

The 8 central Beta-strands in the (beta/alpha)<sub>8</sub> barrel superimpose well between the various known  $\alpha$ -amylase structures, and this part of the structure, including the close surroundings of the active site located at the c-terminal end of the beta-strands, show high similarity between the different amylases.

30

The loops connecting beta-strands and alpha helices display high variations between alpha amylases. These loops constitute the structural context of the active site and the majority of the contacts to the substrate is found among residues located in these loops. Such important characteristics as substrate specificity, substrate binding, pH/activity profile, starch cleavage pattern are determined by the amino acids and the positions of same in these loops.

The substantial differences between the Fungamyl-like  $\alpha$ -amylase structure and the structure of the Termamyl-like  $\alpha$ -amylase disclosed herein which are found in loops 1, 2, 3, and 8 are visualized in the Figures.

5

#### Domain B

The Termamyl-like  $\alpha$ -amylase structure has been found to comprise a special domain structure in the A domain's loop3, also called domain B. The structure of the Termamyl-like  $\alpha$ -amylase B domain has never been seen before in any of the known  $\alpha$ -amylase or ( $\beta$ /alpha)8-barrel proteins.

The domain B structure is a very compact domain having a very high number of charged residues. The B domain arises as an extension of the loop between strand 3 and helix 3 of domain A (shown in Fig. 7) and contains a 5 stranded antiparallel  $\beta$ -sheet structure containing at least one long loop structure and having the connectivity -1, +3, -1X, +2 (Richardson, 1981, Adv. Protein Chem. 34, 167-339).

The first four strands of the B domain form two hairpin loops which twist around each other like a pair of crossed fingers (right-hand twist). The mainchain folds into a  $\beta$ -strand which connects two small  $\beta$ -sheet structures. After making one turn in one sheet it folds back and makes up a two stranded sheet in contact with domain A and an internal hole in the  $\alpha$ -amylase structure. Then the mainchain folds up to a small sheet structure nearly perpendicular to the first two sheets. Before entering the helix 3 on top of the  $\beta$ -strand 3, the approximately 24 last amino acids in domain B form two calcium binding sites in the contact region to domain A.

Domain B is connected with domain A by two peptide stretches, which divide the domain-domain contact areas into two. Domain B is in contact with Domain A by a calcium binding region and an internally buried hole containing waters. Many types of molecular contacts are present. Ionic interacting between acid

and basic amino acids are possible, these interactions are very important for the general stability at high pH and for keeping the Calcium binding sites intact.

#### 5 Domain C

Domain C is the C-terminal part of the protein consisting of amino acids 394-483. Domain C is composed entirely of  $\beta$ -strands which forms a single 8-stranded sheet structure, which folds  
10 back on itself, and thus may be described as a  $\beta$ -sandwich structure. The connectivity is +1,+1, +5, -3, +1, +1, -3 although strands 6 and 7 are only loosely connected. One part of the  $\beta$ -sheet forms the interface to domain A.

#### 15 Ca-binding and Na-binding sites

The structure of the Termamyl-like  $\alpha$ -amylase is remarkable in that it exhibits four calcium-binding sites and one sodium-binding site. In other words four calcium ions and one sodium  
20 ion are found to be present in the structure, although one of the calcium ions displays very weak coordination. Two of the calcium ions form part of a linear cluster of three ions, the central ion being attributed to sodium, which lie at the junction of the A and B domains.

25

The coordinating residues for the calcium ions between the A and B domain are as follows (using the Pdb file nomenclature for amino acid residues and atoms in the Pdb file found in Appendix 1 herein): For the calcium ion nearest to the active  
30 site (IUM 502 in the pdb file), the backbone carbonyls from His235 and Asp194, the sidechain atom OD1 from residues Asp194, Asn102 and Asp200, and one water molecule WAT X3 (atom OW7). For the sodium ion (IUM 505), the binding site includes atom OD2 from Asp194, Asp200, Asp183 and Asp159, and a backbone  
35 carbonyl from Val201. The coordinates for the other calcium ion between domain A and B are (IUM 501) : atom OD2 from Asp204 and Asp159, backbone carbonyl from Asp183 and Ala181, atom OD1 from Asp202, and one water molecule WAT X7 (atom OW7).

One calcium ion is located between the A and C domain, another is located in the C domain. The first mentioned calcium ion, which is also the one best coordinated (IUM 503) includes a carbonyl backbone from Gly300, Tyr302 and His406, atom OD2/OD1 from Asp430, atom OD1 from Asp407, and one water molecule WAT X6 (atom OW7). The other and very weakly coordinated calcium site (IUM 504) comprises 4 water molecules WAT X21 (atom OW8), X6 (atom OW6), X9 (atom OW0) and X28 (atom OW8), OE1/OE2 from Glu447 and OD1 from Asn444.

10

#### *Substrate-binding site*

Without being limited to any theory it is presently believed that favourable interactions between a substrate molecule and the enzyme (such as hydrogen bonds and/or strong electrostatic interaction) are found within a sphere of 4Å of the substrate, when bound to the enzyme. The following residues of the *B. licheniformis*  $\alpha$ -amylase having the amino acid sequence shown in SEQ ID No. 2 are contemplated to be within a distance of 4 Å of the substrate and thus believed to be involved in interactions with the substrate:

Trp13, Tyr14, Asn17, Asp18, Ser50, Gln51, Ala52, Asp53, Val54, Gly55, Tyr56, Lys70, Arg74, Lys76, Val102, His105, Gly107, Gly108, Ala109, Trp138, Thr163, Asp164, Trp165, Asn172, Glu189, Tyr193, Leu196, Met197, Tyr198, Ala199, Arg229, Asp231, Ala232, Lys234, His235, Glu261, Trp263, His327, Asp328, Gln333, Ser334, and Leu335.

The amino acid residues of another Termamyl-like  $\alpha$ -amylase, which are contemplated to be within a distance of 4Å of the substrate, may easily be identified by aligning the amino acid sequence SEQ ID NO 2 with that of the other Termamyl-like  $\alpha$ -amylase and thereby identifying the positions equivalent to those identified above.

35

Generality of structure

Because of the high homology between the various Termamyl-like  $\alpha$ -amylases, the solved structure defined by the coordinates of  
5 Appendix 1 is believed to be representative for the structure of all Termamyl-like  $\alpha$ -amylases. A model structure of other Termamyl-like  $\alpha$ -amylases may easily be built on the basis of the coordinates given in Appendix 1 adapted to the  $\alpha$ -amylase in question by use of an alignment between the respective amino  
10 acid sequences. The creation of a model structure is exemplified in Example 1.

The above identified structurally characteristic parts of the Termamyl-like  $\alpha$ -amylase structure (Ca-binding site, substrate  
15 binding site, loops, etc.) may easily be identified in other Termamyl-like  $\alpha$ -amylases on the basis of a model (or solved) structure of the relevant Termamyl-like  $\alpha$ -amylase or simply on the basis of an alignment between the amino acid sequence of the Termamyl-like  $\alpha$ -amylase in question with that of the *B. licheniformis*  $\alpha$ -amylase used herein for identifying the amino  
20 acid residues of the respective structural elements.

Furthermore, in connection with Termamyl-like variants of the invention, which are defined by modification of specific amino  
25 acid residues of a specific Termamyl-like  $\alpha$ -amylase, it will be understood that variants of another Termamyl-like  $\alpha$ -amylase modified in an equivalent position (as determined from the best possible amino acid sequence alignment between the respective sequences) are intended to be covered as well. Thus,  
30 irrespective of whether an amino acid residue is identified herein for the purpose of defining a structural part of a given  $\alpha$ -amylase or used for identifying a variant of the  $\alpha$ -amylase, this amino acid residue shall be considered as representing the equivalent amino acid residue of any other Termamyl-like  $\alpha$ -  
35 amylase.

Methods of the invention for design of novel  $\alpha$ -amylase variants

In the methods according to the first, second and third aspects of the invention the terms "structure of a Termamyl-like  $\alpha$ -amylase" and "Termamyl-like  $\alpha$ -amylase structure" are intended to indicate the solved structure defined by the coordinates presented in Appendix 1 or a model structure of a given Termamyl-like  $\alpha$ -amylase (such as the *B. licheniformis*  $\alpha$ -amylase) built on the basis of the solved structure.

10

In most cases the parent Termamyl-like  $\alpha$ -amylase to be modified in accordance with the present invention is different from the  $\alpha$ -amylase which was actually used for solving the structure (Appendix 1). This means that the amino acid residue(s) or structural part(s) identified in the solved structure (Appendix 1) in step i) of the method according to the first, second or third aspect of the invention must be translated into the corresponding amino acid residue(s) or structural part(s) of the parent Termamyl-like  $\alpha$ -amylase in question. The "translation" is conveniently performed on the basis of an amino acid sequence alignment between the amino acid sequence of the Termamyl-like  $\alpha$ -amylase used for solving the structure and the amino acid sequence of the parent Termamyl-like  $\alpha$ -amylase in question.

25

The analysis or comparison performed in step i) of the method according to the first, second and third aspect, respectively, of the invention may be performed by use of any suitable computer programme capable of analysing and/or comparing protein structures, e.g. the computer programme Insight, available from Biosym Technologies, Inc. For instance, the basic principle of structure comparison is that the three-dimensional structures to be compared are superimposed on the basis of an alignment of secondary structure elements (such as the central 8  $\beta$ -strands in the barrel) and the parts differing between the structures can subsequently easily be identified from the superimposed structure.

The structural part which is identified in step i) of the methods of the first, second and third aspects of the invention may be composed of one amino acid residue. However, normally the structural part comprises more than one amino acid residue, typically constituting one of the above parts of the Termamyl-like  $\alpha$ -amylase structure such as one of the A, B, or C domains, an interface between any of these domains, a calcium binding site, a loop structure, the substrate binding site, or the like.

10

In the present context the term "structural or functional considerations" is intended to indicate that modifications are made on the basis of an analysis of the relevant structure or structural part and its contemplated impact on the function of the enzyme. Thus, an analysis of the structures of the various  $\alpha$ -amylases, which until now has been elucidated, optionally in combination with an analysis of the functional differences between these  $\alpha$ -amylases, may be used for assigning certain properties of the  $\alpha$ -amylases to certain parts of the  $\alpha$ -amylase structure or to contemplate such relationship. For instance, differences in the pattern or structure of loops surrounding the active site may result in differences in access to the active site of the substrate and thus differences in substrate specificity and/or cleavage pattern. Furthermore, parts of a Termamyl-like  $\alpha$ -amylase involved in or contemplated to be involved in substrate binding (and thus e.g. specificity/cleavage pattern), calcium or sodium ion binding (e.g. of importance for the Calcium-dependency of the enzyme), and the like has been identified (*vide infra*).

30

The modification of an amino acid residue or structural part is typically accomplished by suitable modifications of a DNA sequence encoding the parent enzyme in question. The term "modified" as used in step ii) in the method according to the first aspect of the invention is intended to have the following meaning: When used in relation to an amino acid residue the term is intended to mean replacement of the amino acid residue in question with another amino acid residue. When used in

relation to a structural part, the term is intended to mean replacement of one or more amino acid residues of said structural part, addition of one or more amino acid residues to said part, or deletion of one or more amino acid residues of  
5 said structural part.

The construction of the variant of interest is accomplished by cultivating a microorganism comprising a DNA sequence encoding the variant under conditions which are conducive for producing  
10 the variant, and optionally subsequently recovering the variant from the resulting culture broth. This is described in detail further below.

#### *First aspect of the invention*

15 In a preferred embodiment of the method according to the first aspect of the invention the property of the parent enzyme to be modified is selected from calcium dependency, substrate binding, cleavage pattern, pH dependent activity and the like. Specific examples of how to change these properties of a parent  
20 Termamyl-like  $\alpha$ -amylase are given further below.

In another preferred embodiment the parent Termamyl-like  $\alpha$ -amylase to be modified is a *B. licheniformis*  $\alpha$ -amylase.

#### *25 Second and third aspects of the invention*

One important advantage of the methods according to the second and third aspects of the present invention is that it is possible to adapt the structure (or a structural part) of a Termamyl-like  $\alpha$ -amylase to the structure (or structural part)  
30 of a non-Termamyl-like  $\alpha$ -amylase and *vide versa*. For instance, having identified a loop structure of the non-Termamyl-like  $\alpha$ -amylase which is believed to be responsible for or contributing to a particular property of the non-Termamyl-like  $\alpha$ -amylase it is possible to replace the corresponding structure of the  
35 Termamyl-like  $\alpha$ -amylase with said non-Termamyl-like  $\alpha$ -amylase structure - or if no corresponding structure exists in the Termamyl-like  $\alpha$ -amylase - to insert the structure into the Termamyl-like  $\alpha$ -amylase in such a manner that the resulting

variant Termamyl-like  $\alpha$ -amylase, as far as the relevant part is concerned, resembles the corresponding part of the non-Termamyl-like  $\alpha$ -amylase. When two or more parts of the structure of the parent Termamyl-like  $\alpha$ -amylase are modified so as to resemble the corresponding parts of the non-Termamyl-like  $\alpha$ -amylase it is possible to increase the resemblance to the non-Termamyl-like  $\alpha$ -amylase of the Termamyl-like  $\alpha$ -amylase variant and thus to alter the properties of said variant in the direction of those of said non-Termamyl-like  $\alpha$ -amylase. Loop modifications are discussed in much further detail further below.

Typically, the modification to be performed in step iii) of the method according to the second aspect of the invention is accomplished by deleting one or more amino acid residues of the part of the Termamyl-like  $\alpha$ -amylase to be modified so as to adapt the structure of said part of the parent  $\alpha$ -amylase to the corresponding part of the non-Termamyl-like  $\alpha$ -amylase; by replacing one or more amino acid residues of the part of the Termamyl-like  $\alpha$ -amylase to be modified with the amino acid residues occupying corresponding positions in the non-Termamyl-like  $\alpha$ -amylase; or by insertion of one or more amino acid residues present in the non-Termamyl-like  $\alpha$ -amylase into a corresponding position in the Termamyl-like  $\alpha$ -amylase. For the method according to the third aspect the modification is to be understood analogously, performed on the non-Termamyl-like parent  $\alpha$ -amylase rather than the Termamyl-like  $\alpha$ -amylase.

In step ii) of the method according to the second or third aspect of the invention the part of the structure to be identified is preferably one which in the folded enzyme is believed to be in contact with the substrate (cf the disclosure above in the section entitled "Substrate-binding site) or involved in substrate specificity and/or cleavage pattern, and/or one which is in contact with one of the calcium or sodium ions and/or one, which is contributing to the pH or temperature profile of the enzyme, or one which otherwise, from structural or functional considerations, is contemplated to be

responsible for differences in one or more properties of the Termamyl-like and non-Termamyl-like  $\alpha$ -amylase.

*Non-Termamyl-like  $\alpha$ -amylase*

5 The non-Termamyl-like  $\alpha$ -amylase with which the comparison is made in step i) of the method of the second aspect of the invention and which is the parent  $\alpha$ -amylase in the method of the third aspect of the invention, may be any  $\alpha$ -amylase, which does not belong to the family of Termamyl-like  $\alpha$ -amylases (as  
10 defined above) and, which as a consequence thereof, has a different three-dimensional structure. Furthermore, the non-Termamyl-like  $\alpha$ -amylase should be one which has, at the time that the method is performed, an elucidated or contemplated three-dimensional structure.

15

The non-Termamyl-like  $\alpha$ -amylase may, e.g., be a fungal  $\alpha$ -amylase, a mammalian or a plant  $\alpha$ -amylase or a bacterial  $\alpha$ -amylase (different from a Termamyl-like  $\alpha$ -amylase). Specific examples of such  $\alpha$ -amylases include the *Aspergillus oryzae* TAKA  
20  $\alpha$ -amylase, the *A. niger* acid  $\alpha$ -amylase, the *Bacillus subtilis*  $\alpha$ -amylase, the porcine pancreatic  $\alpha$ -amylase and a barley  $\alpha$ -amylase. All of these  $\alpha$ -amylases have elucidated structures which are clearly different from the structure of the Termamyl-like  $\alpha$ -amylase shown herein.

25

The fungal  $\alpha$ -amylases mentioned above, i.e. derived from *A. niger* and *A. oryzae*, are highly homologous on the amino acid level and generally considered to belong to the same family of  $\alpha$ -amylases. In the present disclosure, this family is termed  
30 "Fungamyl-like  $\alpha$ -amylase" and intends to indicate an  $\alpha$ -amylase which exhibits a high homology, i.e. more than 70%, such as 80% homologous (as defined herein) to the fungal  $\alpha$ -amylase derived from *Aspergillus oryzae*, commercially available as Fungamyl<sup>®</sup>, and the *A. niger*  $\alpha$ -amylase.

35

From the enclosed illustrations of the  $\alpha$ -amylase structure of a Termamyl-like  $\alpha$ -amylase and a comparison of said structure with the structure of a Fungamyl-like  $\alpha$ -amylase it is evident

that major differences exist between the two structures. In the method of the invention it is of particular interest to modify parts of the parent Termamyl-like  $\alpha$ -amylase, which belong to a region with large differences to the Fungamyl-like  $\alpha$ -amylase.

5 In particular, it is of interest to modify the parent Termamyl-like  $\alpha$ -amylase in one or more of the following loops: loop 1, loop 2, loop 3 and/or loop 8 of the parent  $\alpha$ -amylase.

In the method of the third aspect of the invention it is of particular interest to modify loop 1, loop 2, loop 3 and/or loop 8 of the parent non-Termamyl-like  $\alpha$ -amylase to a closer resemblance to the similar loops of a Termamyl-like  $\alpha$ -amylase, such as Termamyl.

15 In the following specific types of variants are described which have been designed by use of the method of the invention.

#### Loop modifications

20 In order to change the substrate specificity of the parent  $\alpha$ -amylase to be modified it is relevant to consider loop modifications. For instance changing one or more of the loop structures of the Termamyl-like  $\alpha$ -amylase into a closer resemblance with the corresponding loop structure(s) of a non-Termamyl-like  $\alpha$ -amylase (such as a Fungamyl-like  $\alpha$ -amylase) it is contemplated that it is possible to change the substrate specificity in the direction of that of the non-Termamyl  $\alpha$ -amylase. In the following different types of loop modifications of interest are listed. It will be understood that the variants

25 may have other changed properties in addition to the modified substrate specificity. It will be understood that the following modifications identified for a specific Termamyl-like  $\alpha$ -amylase are intended to include corresponding modifications in other equivalent positions of other Termamyl-like  $\alpha$ -amylases.

30 Furthermore, it will be understood that, normally, the loop modification will comprise replacement of an entire loop structure or a substantial part thereof in, e.g., the Termamyl-

like  $\alpha$ -amylase, with the corresponding loop structure (or substantial part thereof) in a non-Termamyl-like  $\alpha$ -amylase.

*Loop2 modifications*

- 5 In one embodiment the invention relates to a variant of a parent Termamyl-like  $\alpha$ -amylase, in which variant at least one amino acid residue of the parent  $\alpha$ -amylase, which is/are present in a fragment corresponding to the amino acid fragment 44-57 of the amino acid sequence of SEQ ID No. 4, i.e. loop 2,  
10 has been deleted or replaced with one or more amino acid residues which is/are present in a fragment corresponding to the amino acid fragment 66-84 of the amino acid sequence shown in SEQ ID No. 10, or in which one or more additional amino acid residues has been added using the relevant part of SEQ ID No.  
15 10 or a corresponding part of another Fungamyl-like  $\alpha$ -amylase as a template.

The amino acid sequence shown in SEQ ID No. 10 is the amino acid sequence of the *A. oryzae*  $\alpha$ -amylase, i.e. a Fungamyl-like  
20  $\alpha$ -amylase. It will be understood that amino acid residues or fragments found in corresponding positions in other  $\alpha$ -amylases, in particular Fungamyl-like  $\alpha$ -amylases, may be used as a template for the construction of the variant according to the invention. The corresponding part in other homologous  $\alpha$ -  
25 amylases may easily be identified on the basis of a comparison of the amino acid sequences and/or three-dimensional structures of the respective  $\alpha$ -amylases.

For instance, the variant may be one, which, when the amino  
30 acid sequence of the variant is aligned most closely with the amino acid sequence of the said parent  $\alpha$ -amylase, occupies the same position as the portion from residue X to residue Y of SEQ ID No 4, the said region having at least 80% such as at least 90% sequence homology with the part of SEQ ID No 10 extending  
35 from residue Z to residue V of SEQ ID No 10, wherein X is the amino acid residue occupying position 44, 45, 46, 47 or 48 of SEQ ID No. 4,

Y is the amino acid residue occupying position 51, 52, 53, 54, 55, 56 or 57 of SEQ ID No. 4,

Z is the amino acid residue occupying position 66, 67, 68, 69 or 70 of SEQ ID No. 10, and

5 V is the amino acid residue occupying position 78, 79, 80, 81, 82, 83 or 84 of SEQ ID No. 10.

In other words, the variant may be one in which an amino acid fragment X-Y of the parent  $\alpha$ -amylase, which corresponds to or  
10 is within the amino acid fragment 44-57 of SEQ ID No. 4, has been replaced with an amino acid fragment Z-V, which corresponds to or is within the amino acid fragment 66-84 of the amino acid sequence shown in SEQ ID No. 10, in X, Y, Z and V have the meaning indicated above.

15

A specific example of a variant according to this embodiment is a variant of a parent Termamyl-like  $\alpha$ -amylase, in which the amino acid fragment of the parent  $\alpha$ -amylase, which corresponds to amino acid residues 48-51 of SEQ ID No. 4, has been replaced  
20 with an amino acid fragment corresponding to amino acid residues 70-78 of the amino acid sequence shown in SEQ ID No. 10.

#### *Loop 3 modifications - limited alteration*

25 In another embodiment the invention relates to a variant of a parent Termamyl-like  $\alpha$ -amylase, in which variant at least one of the amino acid residues of the parent  $\alpha$ -amylase, which is/are present in an amino acid fragment corresponding to the amino acid fragment 195-202 of the amino acid sequence of SEQ  
30 ID No. 4, has been deleted or replaced with one or more of the amino acid residues which is/are present in an amino acid fragment corresponding to the amino acid fragment 165-177 of the amino acid sequence shown in SEQ ID No. 10, or in which one or more additional amino acid residues has been added using the  
35 relevant part of SEQ ID No. 10 or a corresponding part of another Fungamyl-like  $\alpha$ -amylase as a template.

For instance, the variant may be one in which an amino acid fragment X-Y of the parent  $\alpha$ -amylase which corresponds to or is within the amino acid fragment 195-202 of SEQ ID No. 4, has been replaced by an amino acid fragment Z-V, which corresponds to or is within the amino acid fragment 165-177 of the amino acid sequence shown in SEQ ID No. 10, in which

X is an amino acid residue corresponding to the amino acid occupying position 195 or 196 of SEQ ID No. 4,

Y is an amino acid residue corresponding to the amino acid occupying position 198, 199, 200, 201, or 202 of SEQ ID No. 4,

Z is an amino acid residue corresponding to the amino acid occupying position 165 or 166 of SEQ ID No. 10, and

V is an amino acid residue corresponding to the amino acid occupying position 173, 174, 175, 176 or 177 of SEQ ID No. 10.

Expressed in another manner, the variant according to this aspect may be one, which, when the amino acid sequence of variant is aligned most closely with the amino acid sequence of the said parent Termamyl-like  $\alpha$ -amylase, occupies the same position as the portion from residue X to residue Y of SEQ ID No 4, the said region having at least 80%, such as 90% sequence homology with the part of SEQ ID No 10 extending from residue Z to residue V of SEQ ID No 10, the meaning of X, Y, Z and V being as identified above.

A specific example of a variant according to this embodiment is a variant of a parent Termamyl-like  $\alpha$ -amylase, in which the amino acid fragment of the parent  $\alpha$ -amylase, which corresponds to amino acid residues 196-198 of SEQ ID No. 4, has been replaced with the amino acid fragment corresponding to amino acid residues 166-173 of the amino acid sequence shown in SEQ ID No. 10.

*Loop 3 modifications - complete domain B*

In a further embodiment the invention relates to a variant of a parent Termamyl-like  $\alpha$ -amylase, in which variant at least one of the amino acid residues of the parent  $\alpha$ -amylase, which is/are present in a fragment corresponding to the amino acid fragment 117-185 of the amino acid sequence of SEQ ID No. 4, has/have been deleted or replaced with one or more of the amino acid residues, which is/are present in an amino acid fragment corresponding to the amino acid fragment 98-210 of the amino acid sequence shown in SEQ ID No. 10, or in which one or more additional amino acid residues has been added using the relevant part of SEQ ID No. 10 or a corresponding part of another Fungamyl-like  $\alpha$ -amylase as a template.

For instance, the variant may be one, in which an amino acid fragment X-Y of the parent  $\alpha$ -amylase, which corresponds to or is within the amino acid fragment 117-185 of SEQ ID No. 4, has been replaced with an amino acid fragment Z-V, which corresponds to or is within the amino acid fragment 98-210 of the amino acid sequence shown in SEQ ID No. 10, in which variant

X is an amino acid residue corresponding to the amino acid occupying position 117, 118, 119, 120 or 121 of SEQ ID No. 4,

25

Y is an amino acid residue corresponding to the amino acid occupying position 181, 182, 183, 184 or 185 of SEQ ID No. 4,

Z is an amino acid residue corresponding to the amino acid occupying position 98, 99, 100, 101, 102 of SEQ ID No. 10, and

30

V is an amino acid residue corresponding to the amino acid occupying position 206, 207, 208, 209 or 210 of SEQ ID No. 10.

A specific example of a variant according to this embodiment is a variant of a parent  $\alpha$ -amylase, in which an amino acid fragment of the parent  $\alpha$ -amylase, which corresponds to amino acid residues 121-181 of SEQ ID No. 4, has been replaced with

the amino acid fragment corresponding to amino acid residues 102-206 of the amino acid sequence shown in SEQ ID No. 10.

In another embodiment the invention relates to a variant of a parent Termamyl-like  $\alpha$ -amylase, in which variant at least one of the amino acid residues of the parent  $\alpha$ -amylase, which is/are present in a fragment corresponding to the amino acid fragment 117-181 of the amino acid sequence of SEQ ID No. 4, has/have been deleted or replaced with one or more of the amino acid residues, which is/are present in an amino acid fragment corresponding to the amino acid fragment to 98-206 of the amino acid sequence shown in SEQ ID No. 10, or in which one or more additional amino acid residues has been added using the relevant part of SEQ ID No. 10 or a corresponding part of another Fungamyl-like  $\alpha$ -amylase as a template.

For instance, the variant may be one, in which the amino acid fragment X-Y of the parent  $\alpha$ -amylase, which corresponds to or is within the amino acid fragment 117-177 of SEQ ID No. 4, has/have been replaced with an amino acid fragment Z-V, which corresponds to or is within the amino acid fragment 98-202 of the amino acid sequence shown in SEQ ID No. 10, in which variant

X is an amino acid residue corresponding to the amino acid occupying position 117, 118, 119, 120 or 121 of SEQ ID No. 4,

Y is an amino acid residue corresponding to the amino acid occupying position 174, 175, 176 or 177 of SEQ ID No. 4,

Z is an amino acid residue corresponding to the amino acid occupying position 98, 99, 100, 101, 102 of SEQ ID No. 10, and

V is an amino acid residue corresponding to the amino acid occupying position 199, 200, 201 or 202 of SEQ ID No. 10.

A specific example of a variant according to this embodiment of the invention is a variant, in which the amino acid fragment of

the parent  $\alpha$ -amylase, which corresponds to amino acid residues 121-174 of SEQ ID No. 4, has been replaced with the amino acid fragment corresponding to amino acid residues 102-199 of the amino acid sequence shown in SEQ ID No. 10.

5

*Loop 1 modifications - minimal addition*

In a further embodiment the present invention relates to a variant of a parent Termamyl-like  $\alpha$ -amylase, in which variant at least one of the amino acid residues of the parent  $\alpha$ -  
10 amylase, which is/are present in an amino acid fragment corresponding to the amino acid fragment 12-19 of the amino acid sequence of SEQ ID No. 4, has/have been deleted or replaced with one or more of the amino acid residues, which is/are present in an amino acid fragment which corresponds to  
15 the amino acid fragment 28-42 of SEQ ID No. 10, or in which one or more additional amino acid residues has/have been inserted using the relevant part of SEQ ID No. 10 or a corresponding part of another Fungamyl-like  $\alpha$ -amylase as a template.

20 For instance, the variant may be one, in which the amino acid fragment X-Y of the parent  $\alpha$ -amylase, which corresponds to or is within the amino acid fragment 12-19 of SEQ ID No. 4, has/have been replaced with an amino acid fragment Z-V, which corresponds to or is within the amino acid fragment 28-42 of  
25 the amino acid sequence shown in SEQ ID No. 10, in which variant

X is an amino acid residue corresponding to the amino acid occupying position 12, 13 or 14 of SEQ ID No. 4,

30

Y is an amino acid residue corresponding to the amino acid occupying position 15, 16, 17, 18 or 19 of SEQ ID No. 4,

Z is an amino acid residue corresponding to the amino acid  
35 occupying position 28, 29, 30, 31 or 32 of SEQ ID No. 10, and

V is an amino acid residue corresponding to the amino acid occupying position 38, 39, 40, 41 or 42 of SEQ ID No. 10.

A specific example of a variant according to this aspect of the invention is a variant, in which the amino acid fragment of the parent  $\alpha$ -amylase, which corresponds to amino acid residues 14-15 of SEQ ID No. 4, has been replaced with the amino acid fragment corresponding to amino acid residues 32-38 of the amino acid sequence shown in SEQ ID No. 10.

*Loop 1 modifications - complete loop*

In a further embodiment the invention relates to a variant of a parent Termamyl-like  $\alpha$ -amylase, in which variant at least one of the amino acid residues of the parent  $\alpha$ -amylase, which is present in a fragment corresponding to amino acid residues 7-23 of the amino acid sequence of SEQ ID No. 4, has/have been deleted or replaced with one or more amino acid residues, which is/are present in an amino acid fragment corresponding to amino acid residues 13-45 of the amino acid sequence shown in SEQ ID No. 10, or in which one or more additional amino acid residues has/have been inserted using the relevant part of SEQ ID No. 10 or a corresponding part of another Fungamyl-like  $\alpha$ -amylase as a template.

For instance, the variant may be one, in which the amino acid fragment X-Y of the parent  $\alpha$ -amylase, which corresponds to or is within the amino acid fragment 7-23 of SEQ ID No. 4, has/have been replaced with an amino acid fragment Z-V, which corresponds to or is within the amino acid fragment 13-45 of the amino acid sequence shown in SEQ ID No. 10, in which variant

X is an amino acid residue corresponding to the amino acid occupying position 7 or 8 of SEQ ID No. 4,

Y is an amino acid residue corresponding to the amino acid occupying position 18, 19, 20, 21, 22 or 23 of SEQ ID No. 4,

Z is an amino acid residue corresponding to the amino acid occupying position 13 or 14 of SEQ ID No. 10, and

V is an amino acid residue corresponding to the amino acid occupying position 40, 41, 42, 43, 44 or 45 of SEQ ID No. 10.

A specific variant according to this embodiment is one, in which the amino acid fragment of the parent  $\alpha$ -amylase, which corresponds to amino acid residues 8-18 of SEQ ID No. 4, has been replaced with the amino acid fragment corresponding to amino acid residues 14-40 of the amino acid sequence shown in SEQ ID No. 10.

10

*Loop 8 modifications*

In a further embodiment the invention relates to a variant of a parent Termamyl-like  $\alpha$ -amylase, in which variant at least one of the amino acid residues of the parent  $\alpha$ -amylase, which is present in a fragment corresponding to amino acid residues 322-346 of the amino acid sequence of SEQ ID No. 2, has/have been deleted or replaced with one or more amino acid residues, which is/are present in an amino acid fragment corresponding to amino acid residues 291-313 of the amino acid sequence shown in SEQ ID No. 10, or in which one or more additional amino acid residues has/have been inserted using the relevant part of SEQ ID No. 10 or a corresponding part of another Fungamyl-like  $\alpha$ -amylase as a template.

For instance, the variant may be one, in which the amino acid fragment X-Y of the parent  $\alpha$ -amylase, which corresponds to or is within the amino acid fragment 322-346 of SEQ ID No. 2, has/have been replaced with an amino acid fragment Z-V, which corresponds to or is within the amino acid fragment 291-313 of the amino acid sequence shown in SEQ ID No. 10, in which variant

X is an amino acid residue corresponding to the amino acid occupying position 322, 323, 324 or 325 of SEQ ID No. 2,

35

Y is an amino acid residue corresponding to the amino acid occupying position 343, 344, 345 or 346 of SEQ ID No. 2,

Z is an amino acid residue corresponding to the amino acid occupying position 291, 292, 293 or 294 of SEQ ID No. 10, and

V is an amino acid residue corresponding to the amino acid occupying position 310, 311, 312 or 313 of SEQ ID No. 10.

A specific variant according to this aspect of the invention is one, in which the amino acid fragment of the parent  $\alpha$ -amylase, which corresponds to amino acid residues 325-345 of SEQ D No. 2, has been replaced with the amino acid fragment corresponding to amino acid residues 294-313 of the amino acid sequence shown in SEQ ID No. 10.

#### Ca<sup>2+</sup> dependency

It is highly desirable to be able to decrease the Ca<sup>2+</sup> dependency of a Termamyl-like  $\alpha$ -amylase. Accordingly, in a further aspect the invention relates to a variant of a parent Termamyl-like  $\alpha$ -amylase, which exhibits  $\alpha$ -amylase activity and which has a decreased Ca<sup>2+</sup> dependency as compared to the parent  $\alpha$ -amylase. The decreased Ca<sup>2+</sup> dependency has the functional result that the variant exhibits a satisfactory amylolytic activity in the presence of a lower concentration of calcium ion in the extraneous medium than is necessary for the parent enzyme and, for example, therefore is less sensitive than the parent to calcium ion-depleting conditions such as those obtained in media containing calcium-complexing agents (such as certain detergent builders).

The decreased Ca<sup>2+</sup> dependency of the variant of the invention may advantageously be achieved by increasing the Ca<sup>2+</sup> binding affinity of the parent Termamyl-like  $\alpha$ -amylase, in other words the stronger the Ca<sup>2+</sup> binding of the enzyme, the lower is the Ca<sup>2+</sup> dependency.

It is presently believed that amino acid residues located within 10Å from a sodium or calcium ion are involved in or are of importance for the Ca<sup>2+</sup> binding capability of the enzyme.

Accordingly, the variant according to this aspect of the invention is preferably one, which has been modified in one or more amino acid residues present within 10Å from a calcium and/or sodium ion identified in the three-dimensional Termamyl-like  $\alpha$ -amylase structure in such a manner that the affinity of the  $\alpha$ -amylase for calcium is increased.

The amino acid residues found within a distance of 10Å from the  $\text{Ca}^{2+}$  binding sites of the *B. licheniformis*  $\alpha$ -amylase with the amino acid sequence SEQ ID NO 2 were determined as described in Example 2 and are as follows:

V102, I103, N104, H105, K106, R125, W155, W157, Y158, H159, F160, D161, G162, T163, Y175, K176, F177, G178, K180, A181, W182, D183, W184, E185, V186, S187, N192, Y193, D194, Y195, L196, M197, Y198, A199, D200, I201, D202, Y203, D204, H205, P206, V208, A209, D231, A232, V233, K234, H235, I236, K237, F238, F240, L241, A294, A295, S296, T297, Q298, G299, G300, G301, Y302, D303, M304, R305, K306, L307, W342, F343, L346, Q393, Y394, Y396, H405, H406, D407, I408, V409, R413, E414, G415, D416, S417, V419, A420, N421, S422, G423, L424, I428, T429, D430, G431, P432, V440, G441, R442, Q443, N444, A445, G446, E447, T448, W449, I462, G475, Y480, V481, Q482, R483.

In order to construct a variant according to this aspect of the invention it is desirable to replace at least one of the above mentioned amino acid residues (or an amino acid residue occupying an equivalent position in another Termamyl-like  $\alpha$ -amylase than that defined by SEQ ID NO 2), which is contemplated to be involved in providing a non-optimal calcium binding, with any other amino acid residue which improves the  $\text{Ca}^{2+}$  binding affinity of the variant enzyme. In practice, the identification and subsequent modification of the amino acid residue is performed by the following method:

- i) identifying an amino acid residue within 10Å from a  $\text{Ca}^{2+}$  binding site of a Termamyl-like  $\alpha$ -amylase structure, which from

structural or functional considerations is believed to be responsible for a non-optimal calcium ion interaction,

ii) constructing a variant in which said amino acid residue is replaced with another amino acid residue which from structural or functional considerations is believed to be important for establishing a higher  $\text{Ca}^{2+}$  binding affinity, and testing the  $\text{Ca}^{2+}$  dependency of the resulting Termamyl-like  $\alpha$ -amylase variant.

10 In the present context, the term "non-optimal calcium ion interaction" is intended to indicate that the amino acid residue in question is selected on the basis of a presumption that substituting said amino acid residue for another may improve a calcium ion binding interaction of the enzyme. For  
15 instance, the amino acid residue in question may be selected on the basis of one or more of the following considerations:

- to obtain an improved interaction between a calcium ion and an amino acid residue located near to the surface of the enzyme  
20 (as identified from the structure of the Termamyl-like  $\alpha$ -amylase). For instance, if the amino acid residue in question is exposed to a surrounding solvent, it may be advantageous to increase the shielding of said amino acid residue from the solvent so as to provide for a stronger interaction between  
25 said amino acid residue and a calcium ion. This can be achieved by replacing said residue (or an amino acid residue in the vicinity of said residue contributing to the shielding) by an amino acid residue which is more bulky or otherwise results in an improved shielding effect.

30

- to stabilize a calcium binding site, for instance by stabilizing the structure of the Termamyl-like  $\alpha$ -amylase (e.g. by stabilizing the contacts between the A, B and C domains or stabilizing one or more of the domains as such). This may,  
35 e.g., be achieved by providing for a better coordination to amino acid side chains, which may, e.g., be obtained by replacing an N residue with a D residue and/or a Q residue with

an E residue (e.g. N104D), e.g. within 10Å, and preferably within 3 or 4Å, of a calcium binding site.

- to protect the calcium binding site or to improve the coordination between the calcium ion and the calcium binding site, e.g. by providing a stronger interaction between the ion and the binding site.

Before actually constructing a Termamyl-like  $\alpha$ -amylase variant according to the above principles it may be convenient to evaluate the contemplated amino acid modification by its accommodation into the Termamyl-like  $\alpha$ -amylase structure, e.g. into a model structure of the parent Termamyl-like  $\alpha$ -amylase.

- Preferably, the amino acid residue to be modified is located within 8Å of a  $\text{Ca}^{2+}$  binding site residue, such as within 5Å of such residue. The amino acid residues within 8Å and 5Å, respectively, may easily be identified by an analogous method used for identifying amino acid residues within 10Å (cf. Example 2).

The following mutation is contemplated to be of particular interest with respect to decreasing the  $\text{Ca}^{2+}$  dependency of a Termamyl-like  $\alpha$ -amylase:

- N104D (of the *B. licheniformis*  $\alpha$ -amylase SEQ ID NO 2, or an equivalent (N to D) mutation of an equivalent position in another Termamyl-like  $\alpha$ -amylase.)

- In connection with substitutions of relevance for  $\text{Ca}^{2+}$  dependency, some other substitutions appear to be of importance in stabilizing the enzyme conformation (for instance the Domains A-B and/or Domains A-C interactions contributing to the overall stability of the enzyme) in that they may, e.g., enhance the strength of binding or retention of calcium ion or sodium ion at or within a calcium or sodium binding site, respectively, within the parent Termamyl-like  $\alpha$ -amylase.

It is desirable to stabilize the C-domain in order to increase the calcium stability and/or thermostability of the enzyme. In this connection the stabilization may result in a stabilization of the binding of calcium by the enzyme, and an improved  
5 contact between the C-domain and the A-domain (of importance for thermostability). The latter may be achieved by introduction of cystein bridges, salt bridges or increase hydrogen, hydrophobic and/or electrostatic interactions.

10 For instance, the C-domain of the *B. licheniformis*  $\alpha$ -amylase having the amino acid sequence shown in SEQ ID No. 2 may be stabilized by introduction of a cystein bridge between domain A and domain C, e.g. by introducing of the following mutations: A349C+I479C and/or L346C+I430C.

15

A salt bridge may be obtained by introduction of the following mutations:

N457D,E

N457D,E+K385R

20 F350D,E+I430R,K

F350D,E+I411R,K

The calcium site of Domain C may be stabilized by replacing the amino acid residues H408 and/or G303 with any other amino acid  
25 residue. Of particular interest is the following mutations:

H408Q,E,N,D and/or G303N,D,Q,E

which are contemplated to provide a better calcium binding or protection from calcium depletion.

30 Similar mutations may be introduced in equivalent positions of other Termamyl-like  $\alpha$ -amylases.

Other substitution mutations (relative to *B. licheniformis*  $\alpha$ -amylase, SEQ ID No. 2) which appear to be of importance,  
35 *inter alia*, in the context of reducing calcium dependency include the following: R23K, H156Y, A181T, A209V and G310D (or equivalent mutations in equivalent positions in another Termamyl-like  $\alpha$ -amylase). Substitutions of R214 and P345 with

other amino acids may also be of importancen in this connection.

Variants with altered activity at higher/lower pH

5

It is contemplated that it is possible to change the pH optima of a Termamyl-like  $\alpha$ -amylase or the enzymatic activity at a given pH by changing the pKa of the active site residues. This may be achieved, e.g. by changing the electrostatic interaction  
10 or hydrophobic interaction between functional groups of amino acid side chains of the amino acid residue to be modified and of its close surroundings. This may, e.g., be accomplished by the following method:

15 i) in a structure of the Termamyl-like  $\alpha$ -amylase in question to identifying an amino acid residue within 15Å from an active site residue, in particuluar 10Å from an active site residue, which amino acid residue is contemplated to be involved in electrostatic or hydrophobic interactions with an active site  
20 residue,

ii) replacing, in the structure, said amino acid residue with an amino acid residue which changes the electrostatic and/or hydrophobic surroundings of an active site residue and  
25 evaluating the accomodation of the amino acid residue in the structure,

iii) optionally repeating step i) and/or ii) until an amino acid replacement has been identified which is accomodated into  
30 the structure,

iv) constructing a Termamyl-like  $\alpha$ -amylase variant resulting from steps i), ii) and optionally iii) and testing the pH dependent enzymatic activity of interest of said variant.

35

In the above method it may be of particular relevance to add a positively charged residue within 5Å of a glutamate (thereby lowering the pKa of the glutamate from about 4.5 to 4), or to

add a negatively charged residue within 5 Å of a glutamate (thereby increasing the pKa to about 5), or to make similar modifications within a distance of about 5Å of a Histidine.

- 5 In a further aspect the invention relates to a variant of a Termamyl-like  $\alpha$ -amylase which exhibits a higher activity at a lower pH (e.g. compared to the pH optimum) than the parent  $\alpha$ -amylase. In particular, the variant comprises a mutation of an amino acid residue corresponding to at least one of the  
10 following positions of the *B. licheniformis*  $\alpha$ -amylase (SEQ ID NO 2):

E336, Q333, P331, I236, V102, A232, I103, L196

The following mutations are of particular interest:

15

E336R,K

Q333R,K

P331R,K

V102R,K,A,T,S,G;

20 I236K,R,N;

I103K,R;

L196K,R;

A232T,S,G;

- 25 or any combination of two or more of these variants or any combination of one or more of these variants with any of the other variants disclosed herein.

- In a still further aspect the invention relates to a variant of  
30 a Termamyl-like  $\alpha$ -amylase which has a higher activity at a higher pH than the parent  $\alpha$ -amylase. In particular, the variant comprises a mutation of an amino acid residue corresponding to at least one of the following positions of the *B. licheniformis*  $\alpha$ -amylase (SEQ ID NO 2):

35

N236, H281, Y273

In particular, the variant comprises a mutation corresponding to at least one of the following mutations of the *B. licheniformis*  $\alpha$ -amylase (SEQ ID NO 2):

5 N326I,Y,F,L,V  
H281F,I,L  
Y273F,W

or any combination of two or more of these variants or any  
10 combination of one or more of these variants with any of  
the other variants disclosed herein.

A mutation which appears to be importance in relation to the specific activity of variants of the invention is a mutation  
15 corresponding to the substitution S187D in *B. licheniformis*  $\alpha$ -amylase (SEQ ID NO 2).

Variants with increased thermostability and/or altered temperature optimum

20 In a further desired aspect the invention relates to a variant of a parent Termamyl-like  $\alpha$ -amylase, which variant is the result of one or more amino acid residues having been deleted from, replaced or added to the parent  $\alpha$ -amylase so as to obtain  
25 an increased thermostability of the variant.

The Termamyl-like  $\alpha$ -amylase structure contains a number of unique internal holes, which may contain water, and a number of crevices. In order to increase the thermostability of the  $\alpha$ -  
30 amylase it may be desirable to reduce the number of holes and crevices (or reduce the size of the holes or crevices), e.g. by introducing one or more hydrophobic contacts, preferably achieved by introducing bulkier residues, in the vicinity or surroundings of the hole. For instance, the amino acid residues  
35 to be modified are those which are involved in the formation of the hole.

Accordingly, in a further aspect the present invention relates to a method of increasing the thermostability and/or altering the temperature optimum of a parent Termamyl-like  $\alpha$ -amylase, which method comprises

5

i) identifying an internal hole or a crevice of the parent Termamyl-like  $\alpha$ -amylase in the three-dimensional structure of said  $\alpha$ -amylase,

10 ii) replacing, in the structure, one or more amino acid residues in the neighbourhood of the hole or crevice identified in i) with another amino acid residue which from structural or functional considerations is believed to increase the hydrophobic interaction and to fill out or reduce the size of  
15 the hole or crevice,

iii) constructing a Termamyl-like  $\alpha$ -amylase variant resulting from step ii) and testing the thermostability and/or temperature optimum of the variant.

20 The structure used for identifying the hole or crevice of the parent Termamyl-like  $\alpha$ -amylase may be the structure identified in Appendix 1 or a model structure of the parent Termamyl-like  $\alpha$ -amylase built thereon.

25 It will be understood that the hole or crevice is identified by the amino acid residues surrounding the hole/crevice, and that modification of said amino acid residues are of importance for filling or reducing the size of the hole/crevice. The particular amino acid residues referred to below are those  
30 which in crystal structure have been found to flank the hole/crevice in question.

In order to fill (completely or partly) a major hole located between domain A and B, mutation to any other amino acid  
35 residue of an amino acid residue corresponding to one or more of the following residues of the *B. licheniformis*  $\alpha$ -amylase (SEQ ID NO 2) is contemplated:

L61, Y62, F67, K106, G145, I212, S151, R214, Y150, F143,  
R146

5

Of particular interest is a mutation to a more bulky amino acid residue than the amino acid residue of the parent enzyme.

Of particular interest is a variant of a Termamyl-like  $\alpha$ -  
10 amylase which comprises a mutation corresponding to the following mutations (using the numbering of *B. licheniformis*  $\alpha$ -amylase (SEQ ID NO 2):

L61W,V,F;

15 Y62W;

F67W;

K106R,F,W;

G145F,W

I212F,L,W,Y,R,K;

20 S151 replaced with any other amino acid residue and in particular with F,W,I or L;

R214W;

Y150R,K;

F143W; and/or

25 R146W.

In order to fill a hole in the vicinity of the active site mutation to any other amino acid residue of an amino acid residue corresponding to one or more of the following residues  
30 of the *B. licheniformis*  $\alpha$ -amylase (SEQ ID NO 2) is contemplated:

L241, I236.

35 Of interest is a mutation to a more bulky amino acid residue.

Of particular interest is a variant of a Termamyl-like  $\alpha$ -amylase which comprises a mutation corresponding to one or more of the following mutations in the *B. licheniformis*  $\alpha$ -amylase:

- 5 L241I,F,Y,W; and/or  
I236L,F,W,Y

In order to fill a hole in the vicinity of the active site mutation to any other amino acid residue of an amino acid  
10 residue corresponding to one or more of the following residues of the *B. licheniformis*  $\alpha$ -amylase (SEQ ID NO 2) is contemplated:  
L7, V259, F284

- 15 Of interest is a mutation to a more bulky amino acid residue.

Of particular interest is a variant of a Termamyl-like  $\alpha$ -amylase which comprises a mutation corresponding to one or more of the following mutations in the *B. licheniformis*  $\alpha$ -amylase:

- 20 L7F,I,W  
V259F,I,L  
F284W

- 25 In order to fill a hole in the vicinity of the active site mutation to any other amino acid residue of an amino acid residue corresponding to one or more of the following residues of the *B. licheniformis*  $\alpha$ -amylase (SEQ ID NO 2) is contemplated:

- 30 F350, F343

Of interest is a mutation to a more bulky amino acid residue.

- 35 Of particular interest is a variant of a Termamyl-like  $\alpha$ -amylase which comprises a mutation corresponding to one or more of the following mutations in the *B. licheniformis*  $\alpha$ -amylase:  
F350W

F343W

In order to fill a hole in the vicinity of the active site mutation to any other amino acid residue of an amino acid residue corresponding to one or more of the following residues of the *B. licheniformis*  $\alpha$ -amylase (SEQ ID NO 2) is contemplated:

L427, V481

10

Of interest is a mutation to a more bulky amino acid residue.

Of particular interest is a variant of a Termamyl-like  $\alpha$ -amylase which comprises a mutation corresponding to one or more of the following mutations in the *B. licheniformis*  $\alpha$ -amylase:

L427F,L,W

V481,F,I,L,W

20 Variants with an altered cleavage pattern

In the starch liquefaction process it is desirable to use an  $\alpha$ -amylase which is capable of degrading the starch molecules into long branched oligo saccharides (like, e.g. the Fungamyl-like  $\alpha$ -amylases) rather than shorter branched oligo saccharides (like conventional Termamyl-like  $\alpha$ -amylases). The resulting very small branched oligosaccharides (panose precursors) cannot be hydrolyzed properly by pullulanases, which in the liquefaction process are used after the  $\alpha$ -amylases and before the amyloglucosidases. Thus, in the presence of panose precursors the action of amylo-glucoamylase ends up with a high degree of the small branched limiting-dextrin, the trisaccharide panose. The presence of panose lowers the saccharification yield significantly and is thus undesirable.

35 Thus, one aim of the present invention is to change the degradation characteristics of a Termamyl-like  $\alpha$ -amylase to that of a Fungamyl-like  $\alpha$ -amylases without at the same time reducing the thermostability of the Termamyl-like  $\alpha$ -amylase.

Accordingly, in a further aspect the invention relates to a variant of a Termamyl-like  $\alpha$ -amylase which has a reduced ability to cleave a substrate close to the branching point.

5 The variant may suitably be constructed by a method which comprises

i) identifying the substrate binding area of the parent Termamyl-like  $\alpha$ -amylase in a model of the three-dimensional  
10 structure of said  $\alpha$ -amylase, (e.g. within a sphere of 4Å from the substrate binding site (as defined in the section above entitled "Substrate Binding Site"),

ii) replacing, in the model, one or more amino acid residues of  
15 the substrate binding area of the cleft identified in i), which is/are believed to be responsible for the cleavage pattern of the parent  $\alpha$ -amylase, with another amino acid residue which from structural considerations is believed to result in an altered substrate cleavage pattern, or deleting one or more  
20 amino acid residues of the substrate binding area contemplated to introduce favourable interactions to the substrate or adding one or more amino acid residues to the substrate binding area contemplated to introduce favourable interactions to the substrate, and

25 iii) constructing a Termamyl-like  $\alpha$ -amylase variant resulting from step ii) and testing the substrate cleavage pattern of the variant.

Of particular interest is a variant which cleaves an  
30 amylopectin substrate, from the reducing end, more than one glucose unit from the branching point, preferably more than two or three glucose units from the branching point, i.e. at a further distance from the branching point than that obtained by use of a wild type *B. licheniformis*  $\alpha$ -amylase.

35

Residues of particular interest in connection with this aspect of the invention correspond to the following residues of the *B. licheniformis*  $\alpha$ -amylase (SEQ ID NO 2): V54, D53, Y56, Q333,

G57, and the variants according to this aspect preferably comprises a mutation in one or more of these residues.

In particular, the variant comprises at least one of the following mutations, which are expected to prevent cleavage close to the branching point:

V54L,I,F,Y,W,R,K,H,E,Q

D53L,I,F,Y,W

10 Y56W

Q333W

G57all possible amino acid residues

A52amino acid residues larger than A, e.g. A52W,Y,L,F,I.

15 Variants of a fungal  $\alpha$ -amylase

In a still further embodiment the invention relates to a variant of a parent Fungamyl-like  $\alpha$ -amylase, in which variant at least one of the amino acid residues of the parent  $\alpha$ -amylase, which is/are present in an amino acid fragment corresponding to amino acid residues 291-313 of the amino acid sequence of SEQ ID No. 10, has/have been deleted or replaced with one or more of the amino acid residues, which is/are present in an amino acid fragment corresponding to amino acid residues 98-210 of the amino acid sequence shown in SEQ ID No. 4, or in which one or more additional amino acid residues has/have been inserted using the relevant part of SEQ ID No. 4 or a corresponding part of another Termamyl-like  $\alpha$ -amylase as a template.

30

For instance, the variant may be one, in which the amino acid fragment X-Y of the parent  $\alpha$ -amylase, which corresponds to or is within the amino acid fragment 117-185 of SEQ ID No. 10, has/have been replaced with an amino acid fragment Z-V, which corresponds to or is within the amino acid fragment 98-210 of the amino acid sequence shown in SEQ ID No. 4, in which variant

X is an amino acid residue corresponding to the amino acid occupying position 117, 118, 119, 120 or 121 of SEQ ID No. 10,

Y is an amino acid residue corresponding to the amino acid occupying position 181, 182, 183, 184 or 185 of SEQ ID No. 10,

Z is an amino acid residue corresponding to the amino acid occupying position 98, 99, 100, 101 or 102 of SEQ ID No. 4, and

10 V is an amino acid residue corresponding to the amino acid occupying position 206, 207, 208, 209 or 210 of SEQ ID No. 4.

A specific example of a variant according to this aspect of the invention is one, in which the amino acid fragment of the parent  $\alpha$ -amylase, which corresponds to amino acid residues 121-181 of SEQ ID No. 10, has been replaced with the amino acid fragment corresponding to amino acid residues 102-206 of the amino acid sequence shown in SEQ ID No. 4.

20 Another example of a variant according to this aspect of the invention is one, in which the amino acid fragment of the parent  $\alpha$ -amylase, which corresponds to amino acid residues 121-174 of SEQ ID No. 10, has been replaced with the amino acid fragment corresponding to amino acid residues 102-199 of the amino acid sequence shown in SEQ ID No. 4.

In a further embodiment the invention relates to a variant of a parent Fungamyl-like  $\alpha$ -amylase, in which an amino acid fragment corresponding to amino acid residues 181-184 of the amino acid sequence shown in SEQ ID No. 10 has been deleted.

#### General mutations in variants of the invention

It may be preferred that the variant of the invention comprises one or more modifications in addition to those outlined above. Thus, it may be advantageous that one or more proline residues present in the part of the  $\alpha$ -amylase variant

having been modified is/are replaced with a non-proline residue which may be any of the possible, naturally occurring non-proline residues, and which preferably is an alanine, glycine, serine, threonine, valine or leucine.

5 Analogously, it may be preferred that one or more cysteine residues present in the amino acid residues with which the parent  $\alpha$ -amylase is modified are replaced with a non-cysteine residues such as serine, alanine, threonine, glycine, valine or  
10 leucine.

Furthermore, the variant of the invention may either as the only modification or in combination with any of the above outlined modifications be modified so that one or more Asp  
15 and/or Glu present in an amino acid fragment corresponding to the amino acid fragment 185-209 of SEQ ID No. 8 is replaced by an Asn and/or Gln, respectively. Also of interest is the modification of one or more of the Lys residues present in the Termamyl-like  $\alpha$ -amylase is replaced by an Arg present in an  
20 amino acid fragment corresponding to the amino acid fragment 185-209 of SEQ ID No. 8 is replaced by an Asn and/or Gln, respectively.

It will be understood that in accordance with the present  
25 invention variants may be prepared which carry two or more of the above outlined modifications. For instance, variants may be prepared which comprises a modification in the loop 1 and loop 2 region, a modification in loop 2 and limited loop 3, a modification in loop 1, loop 2, loop 3 and loop 8, etc.

30 Furthermore, it may be advantageous to introduce point-mutations in any of the variants described herein.

#### Methods of preparing $\alpha$ -amylase variants

35 Several methods for introducing mutations into genes are known in the art. After a brief discussion of the cloning of  $\alpha$ -amylase-encoding DNA sequences, methods for generating

mutations at specific sites within the  $\alpha$ -amylase-encoding sequence will be discussed.

Cloning a DNA sequence encoding an  $\alpha$ -amylase

- 5 The DNA sequence encoding a parent  $\alpha$ -amylase may be isolated from any cell or microorganism producing the  $\alpha$ -amylase in question, using various methods well known in the art. First, a genomic DNA and/or cDNA library should be constructed using chromosomal DNA or messenger RNA from the organism that produces the  $\alpha$ -amylase to be studied. Then, if the amino acid sequence of the  $\alpha$ -amylase is known, homologous, labelled oligonucleotide probes may be synthesized and used to identify  $\alpha$ -amylase-encoding clones from a genomic library prepared from the organism in question. Alternatively, a labelled oligonucleotide probe containing sequences homologous to a known  $\alpha$ -amylase gene could be used as a probe to identify  $\alpha$ -amylase-encoding clones, using hybridization and washing conditions of lower stringency.
- 20 Yet another method for identifying  $\alpha$ -amylase-encoding clones would involve inserting fragments of genomic DNA into an expression vector, such as a plasmid, transforming  $\alpha$ -amylase-negative bacteria with the resulting genomic DNA library, and then plating the transformed bacteria onto agar containing a substrate for  $\alpha$ -amylase, thereby allowing clones expressing the  $\alpha$ -amylase to be identified.

Alternatively, the DNA sequence encoding the enzyme may be prepared synthetically by established standard methods, e.g. the phosphoroamidite method described by S.L. Beaucage and M.H. Caruthers (1981) or the method described by Matthes et al. (1984). In the phosphoroamidite method, oligonucleotides are synthesized, e.g. in an automatic DNA synthesizer, purified, annealed, ligated and cloned in appropriate vectors.

35 Finally, the DNA sequence may be of mixed genomic and synthetic origin, mixed synthetic and cDNA origin or mixed genomic and cDNA origin, prepared by ligating fragments of synthetic,

genomic or cDNA origin (as appropriate, the fragments corresponding to various parts of the entire DNA sequence), in accordance with standard techniques. The DNA sequence may also be prepared by polymerase chain reaction (PCR) using specific  
5 primers, for instance as described in US 4,683,202 or R.K. Saiki et al. (1988).

#### Site-directed mutagenesis

Once an  $\alpha$ -amylase-encoding DNA sequence has been isolated, and  
10 desirable sites for mutation identified, mutations may be introduced using synthetic oligonucleotides. These oligonucleotides contain nucleotide sequences flanking the desired mutation sites; mutant nucleotides are inserted during oligonucleotide synthesis. In a specific method, a single-stranded  
15 gap of DNA, bridging the  $\alpha$ -amylase-encoding sequence, is created in a vector carrying the  $\alpha$ -amylase gene. Then the synthetic nucleotide, bearing the desired mutation, is annealed to a homologous portion of the single-stranded DNA. The remaining gap is then filled in with DNA polymerase I (Klenow fragment)  
20 and the construct is ligated using T4 ligase. A specific example of this method is described in Morinaga et al. (1984). US 4,760,025 discloses the introduction of oligonucleotides encoding multiple mutations by performing minor alterations of the cassette. However, an even greater variety of mutations can  
25 be introduced at any one time by the Morinaga method, because a multitude of oligonucleotides, of various lengths, can be introduced.

Another method of introducing mutations into  $\alpha$ -amylase-encoding  
30 DNA sequences is described in Nelson and Long (1989). It involves the 3-step generation of a PCR fragment containing the desired mutation introduced by using a chemically synthesized DNA strand as one of the primers in the PCR reactions. From the PCR-generated fragment, a DNA fragment carrying the mutation  
35 may be isolated by cleavage with restriction endonucleases and reinserted into an expression plasmid.

#### Random mutagenesis

Random mutagenesis is suitably performed either as localized or region-specific random mutagenesis in at least three parts of the gene translating to the amino acid sequence shown in question, or within the whole gene.

- 5 For region-specific random mutagenesis with a view to improving the thermal stability of a parent Termamyl-like  $\alpha$ -amylase, codon positions corresponding to the following amino acid residues of the *B. licheniformis*  $\alpha$ -amylase (SEQ ID NO 2) may  
10 appropriately be targeted:

To improve the stability of the calcium site between Domain A and C

- I428-A435  
15 T297-L308  
F403-V409

To improve the stability between domain A and B:

- D180-D204  
20 H156-T163  
A232-F238

- With a view to achieving improved binding of a substrate (i.e. improved binding of a carbohydrate species, such as amylose or  
25 amylopectin) by a Termamyl-like  $\alpha$ -amylase variant, modified (e.g. higher) substrate specificity and/or modified (e.g. higher) specificity with respect to cleavage (hydrolysis) of substrate, it appears that the following codon positions for the amino acid sequence shown in SEQ ID NO 2 (or equivalent  
30 codon positions for another parent Termamyl-like  $\alpha$ -amylase in the context of the invention) may particularly appropriately be targeted:

- 13-18  
35 50-56  
70-76  
102-109  
163-172

189-199

229-235

360-264

327-335

5

The random mutagenesis of a DNA sequence encoding a parent  $\alpha$ -amylase to be performed in accordance with step a) of the above-described method of the invention may conveniently be performed by use of any method known in the art.

10

For instance, the random mutagenesis may be performed by use of a suitable physical or chemical mutagenizing agent, by use of a suitable oligonucleotide, or by subjecting the DNA sequence to PCR generated mutagenesis. Furthermore, the random mutagenesis may be performed by use of any combination of these mutagenizing agents.

The mutagenizing agent may, e.g., be one which induces transitions, transversions, inversions, scrambling, deletions, and/or insertions.

Examples of a physical or chemical mutagenizing agent suitable for the present purpose include ultraviolet (UV) irradiation, hydroxylamine, N-methyl-N'-nitro-N-nitrosoguanidine (MNNG), O-methyl hydroxylamine, nitrous acid, ethyl methane sulphonate (EMS), sodium bisulphite, formic acid, and nucleotide analogues.

When such agents are used, the mutagenesis is typically performed by incubating the DNA sequence encoding the parent enzyme to be mutagenized in the presence of the mutagenizing agent of choice under suitable conditions for the mutagenesis to take place, and selecting for mutated DNA having the desired properties.

35

When the mutagenesis is performed by the use of an oligonucleotide, the oligonucleotide may be doped or spiked with the three non-parent nucleotides during the synthesis of the oligonucleo-

tide at the positions which are to be changed. The doping or spiking may be done so that codons for unwanted amino acids are avoided. The doped or spiked oligonucleotide can be incorporated into the DNA encoding the amylolytic enzyme by any published technique, using e.g. PCR, LCR or any DNA polymerase and ligase.

When PCR-generated mutagenesis is used, either a chemically treated or non-treated gene encoding a parent  $\alpha$ -amylase enzyme is subjected to PCR under conditions that increase the mis-incorporation of nucleotides (Deshler 1992; Leung et al., Technique, Vol.1, 1989, pp. 11-15).

A mutator strain of *E. coli* (Fowler et al., Molec. Gen. Genet., 133, 1974, pp. 179-191), *S. cerevisiae* or any other microbial organism may be used for the random mutagenesis of the DNA encoding the amylolytic enzyme by e.g. transforming a plasmid containing the parent enzyme into the mutator strain, growing the mutator strain with the plasmid and isolating the mutated plasmid from the mutator strain. The mutated plasmid may subsequently be transformed into the expression organism.

The DNA sequence to be mutagenized may conveniently be present in a genomic or cDNA library prepared from an organism expressing the parent amylolytic enzyme. Alternatively, the DNA sequence may be present on a suitable vector such as a plasmid or a bacteriophage, which as such may be incubated with or otherwise exposed to the mutagenizing agent. The DNA to be mutagenized may also be present in a host cell either by being integrated in the genome of said cell or by being present on a vector harboured in the cell. Finally, the DNA to be mutagenized may be in isolated form. It will be understood that the DNA sequence to be subjected to random mutagenesis is preferably a cDNA or a genomic DNA sequence.

In some cases it may be convenient to amplify the mutated DNA sequence prior to the expression step (b) or the screening step (c) being performed. Such amplification may be performed in

accordance with methods known in the art, the presently preferred method being PCR-generated amplification using oligonucleotide primers prepared on the basis of the DNA or amino acid sequence of the parent enzyme.

5

Subsequent to the incubation with or exposure to the mutagenizing agent, the mutated DNA is expressed by culturing a suitable host cell carrying the DNA sequence under conditions allowing expression to take place. The host cell used for this purpose may be one which has been transformed with the mutated DNA sequence, optionally present on a vector, or one which was carried the DNA sequence encoding the parent enzyme during the mutagenesis treatment. Examples of suitable host cells are the following: grampositive bacteria such as *Bacillus subtilis*,  
15 *Bacillus licheniformis*, *Bacillus lentus*, *Bacillus brevis*, *Bacillus stearothermophilus*, *Bacillus alkalophilus*, *Bacillus amyloliquefaciens*, *Bacillus coagulans*, *Bacillus circulans*, *Bacillus lautus*, *Bacillus megaterium*, *Bacillus thuringiensis*, *Streptomyces lividans* or *Streptomyces murinus*; and gramnegative  
20 bacteria such as *E.coli*.

The mutated DNA sequence may further comprise a DNA sequence encoding functions permitting expression of the mutated DNA sequence.

25

Localized random mutagenesis: the random mutagenesis may advantageously be localized to a part of the parent  $\alpha$ -amylase in question. This may, e.g., be advantageous when certain regions of the enzyme have been identified to be of particular  
30 importance for a given property of the enzyme, and when modified are expected to result in a variant having improved properties. Such regions may normally be identified when the tertiary structure of the parent enzyme has been elucidated and related to the function of the enzyme.

35

The localized random mutagenesis is conveniently performed by use of PCR-generated mutagenesis techniques as described above or any other suitable technique known in the art.

Alternatively, the DNA sequence encoding the part of the DNA sequence to be modified may be isolated, e.g. by being inserted into a suitable vector, and said part may subsequently be subjected to mutagenesis by use of any of the mutagenesis methods discussed above.

With respect to the screening step in the above-mentioned method of the invention, this may conveniently be performed by use of a filter assay based on the following principle:

10

A microorganism capable of expressing the mutated amylolytic enzyme of interest is incubated on a suitable medium and under suitable conditions for the enzyme to be secreted, the medium being provided with a double filter comprising a first protein-binding filter and on top of that a second filter exhibiting a low protein binding capability. The microorganism is located on the second filter. Subsequent to the incubation, the first filter comprising enzymes secreted from the microorganisms is separated from the second filter comprising the microorganisms.

15

20 The first filter is subjected to screening for the desired enzymatic activity and the corresponding microbial colonies present on the second filter are identified.

The filter used for binding the enzymatic activity may be any protein binding filter e.g. nylon or nitrocellulose. The top-filter carrying the colonies of the expression organism may be any filter that has no or low affinity for binding proteins e.g. cellulose acetate or Durapore™. The filter may be pretreated with any of the conditions to be used for screening or may be treated during the detection of enzymatic activity.

25

30

The enzymatic activity may be detected by a dye, fluorescence, precipitation, pH indicator, IR-absorbance or any other known technique for detection of enzymatic activity.

35

The detecting compound may be immobilized by any immobilizing agent e.g. agarose, agar, gelatine, polyacrylamide, starch, filter paper, cloth; or any combination of immobilizing agents.

$\alpha$ -Amylase activity is detected by Cibacron Red labelled amylopectin, which is immobilized on agarose. For screening for variants with increased thermal and high-pH stability, the filter with bound  $\alpha$ -amylase variants is incubated in a buffer at pH 10.5 and 60° or 65°C for a specified time, rinsed briefly in deionized water and placed on the amylopectin-agarose matrix for activity detection. Residual activity is seen as lysis of Cibacron Red by amylopectin degradation. The conditions are chosen to be such that activity due to the  $\alpha$ -amylase having the amino acid sequence shown in SEQ ID No.1 can barely be detected. Stabilized variants show, under the same conditions, increased colour intensity due to increased liberation of Cibacron Red.

For screening for variants with an activity optimum at a lower temperature and/or over a broader temperature range, the filter with bound variants is placed directly on the amylopectin-Cibacron Red substrate plate and incubated at the desired temperature (e.g. 4°C, 10°C or 30°C) for a specified time. After this time activity due to the  $\alpha$ -amylase having the amino acid sequence shown in SEQ ID No.1 can barely be detected, whereas variants with optimum activity at a lower temperature will show increase amylopectin lysis. Prior to incubation onto the amylopectin matrix, incubation in all kinds of desired media - e.g. solutions containing Ca<sup>2+</sup>, detergents, EDTA or other relevant additives - can be carried out in order to screen for changed dependency or for reaction of the variants in question with such additives.

30

#### Testing of variants of the invention

The testing of variants of the invention may suitably be performed by determining the starch-degrading activity of the variant, for instance by growing host cells transformed with a DNA sequence encoding a variant on a starch-containing agarose plate and identifying starch-degrading host cells. Further testing as to altered properties (including specific activity,

substrate specificity, cleavage pattern, thermoactivation, pH optimum, pH dependency, temperature optimum, and any other parameter) may be performed in accordance with methods known in the art.

5

#### Expression of $\alpha$ -amylase variants

According to the invention, a DNA sequence encoding the variant produced by methods described above, or by any alternative methods known in the art, can be expressed, in enzyme form, using an expression vector which typically includes control sequences encoding a promoter, operator, ribosome binding site, translation initiation signal, and, optionally, a repressor gene or various activator genes.

15 The recombinant expression vector carrying the DNA sequence encoding an  $\alpha$ -amylase variant of the invention may be any vector which may conveniently be subjected to recombinant DNA procedures, and the choice of vector will often depend on the host cell into which it is to be introduced. Thus, the vector may be an autonomously replicating vector, i.e. a vector which exists as an extrachromosomal entity, the replication of which is independent of chromosomal replication, e.g. a plasmid, a bacteriophage or an extrachromosomal element, minichromosome or an artificial chromosome. Alternatively, the vector may be one which, when introduced into a host cell, is integrated into the host cell genome and replicated together with the chromosome(s) into which it has been integrated.

In the vector, the DNA sequence should be operably connected to a suitable promoter sequence. The promoter may be any DNA sequence which shows transcriptional activity in the host cell of choice and may be derived from genes encoding proteins either homologous or heterologous to the host cell. Examples of suitable promoters for directing the transcription of the DNA sequence encoding an  $\alpha$ -amylase variant of the invention, especially in a bacterial host, are the promoter of the lac operon of *E. coli*, the *Streptomyces coelicolor* agarase gene *dagA* promoters, the promoters of the *Bacillus licheniformis*  $\alpha$ -

amylase gene (*amyL*), the promoters of the *Bacillus stearothermophilus* maltogenic amylase gene (*amyM*), the promoters of the *Bacillus amyloliquefaciens*  $\alpha$ -amylase (*amyQ*), the promoters of the *Bacillus subtilis* *xylA* and *xylB* genes etc. For  
transcription in a fungal host, examples of useful promoters  
are those derived from the gene encoding *A. oryzae* TAKA  
amylase, *Rhizomucor miehei* aspartic proteinase, *A. niger* neutral  $\alpha$ -amylase, *A. niger* acid stable  $\alpha$ -amylase, *A. niger* glucoamylase, *Rhizomucor miehei* lipase, *A. oryzae* alkaline  
protease, *A. oryzae* triose phosphate isomerase or *A. nidulans* acetamidase.

The expression vector of the invention may also comprise a suitable transcription terminator and, in eukaryotes, polyadenylation sequences operably connected to the DNA sequence encoding the  $\alpha$ -amylase variant of the invention. Termination and polyadenylation sequences may suitably be derived from the same sources as the promoter.

The vector may further comprise a DNA sequence enabling the vector to replicate in the host cell in question. Examples of such sequences are the origins of replication of plasmids pUC19, pACYC177, pUB110, pE194, pAMB1 and pIJ702.

The vector may also comprise a selectable marker, e.g. a gene the product of which complements a defect in the host cell, such as the *dal* genes from *B. subtilis* or *B. licheniformis*, or one which confers antibiotic resistance such as ampicillin, kanamycin, chloramphenicol or tetracyclin resistance. Furthermore, the vector may comprise *Aspergillus* selection markers such as *amdS*, *argB*, *niaD* and *sC*, a marker giving rise to hygromycin resistance, or the selection may be accomplished by co-transformation, e.g. as described in WO 91/17243.

While intracellular expression may be advantageous in some respects, e.g. when using certain bacteria as host cells, it is generally preferred that the expression is extracellular. In general, the *Bacillus*  $\alpha$ -amylases mentioned herein comprise a

preregion permitting secretion of the expressed protease into the culture medium. If desirable, this preregion may be replaced by a different preregion or signal sequence, conveniently accomplished by substitution of the DNA sequences encoding the respective preregions.

The procedures used to ligate the DNA construct of the invention encoding an  $\alpha$ -amylase variant, the promoter, terminator and other elements, respectively, and to insert them into suitable vectors containing the information necessary for replication, are well known to persons skilled in the art (cf., for instance, Sambrook et al. (1989)).

The cell of the invention, either comprising a DNA construct or an expression vector of the invention as defined above, is advantageously used as a host cell in the recombinant production of an  $\alpha$ -amylase variant of the invention. The cell may be transformed with the DNA construct of the invention encoding the variant, conveniently by integrating the DNA construct (in one or more copies) in the host chromosome. This integration is generally considered to be an advantage as the DNA sequence is more likely to be stably maintained in the cell. Integration of the DNA constructs into the host chromosome may be performed according to conventional methods, e.g. by homologous or heterologous recombination. Alternatively, the cell may be transformed with an expression vector as described above in connection with the different types of host cells.

The cell of the invention may be a cell of a higher organism such as a mammal or an insect, but is preferably a microbial cell, e.g. a bacterial or a fungal (including yeast) cell.

Examples of suitable bacteria are grampositive bacteria such as *Bacillus subtilis*, *Bacillus licheniformis*, *Bacillus lentus*, *Bacillus brevis*, *Bacillus stearothermophilus*, *Bacillus alkalophilus*, *Bacillus amyloliquefaciens*, *Bacillus coagulans*, *Bacillus circulans*, *Bacillus lautus*, *Bacillus megaterium*, *Bacillus thuringiensis*, or *Streptomyces lividans* or *Streptomyces*

*murinus*, or gramnegative bacteria such as *E.coli*. The transformation of the bacteria may, for instance, be effected by protoplast transformation or by using competent cells in a manner known *per se*.

5

The yeast organism may favourably be selected from a species of *Saccharomyces* or *Schizosaccharomyces*, e.g. *Saccharomyces cerevisiae*. The filamentous fungus may advantageously belong to a species of *Aspergillus*, e.g. *Aspergillus oryzae* or *Aspergillus niger*. Fungal cells may be transformed by a process involving protoplast formation and transformation of the protoplasts followed by regeneration of the cell wall in a manner known *per se*. A suitable procedure for transformation of *Aspergillus* host cells is described in EP 238 023.

15

In a yet further aspect, the present invention relates to a method of producing an  $\alpha$ -amylase variant of the invention, which method comprises cultivating a host cell as described above under conditions conducive to the production of the variant and recovering the variant from the cells and/or culture medium.

The medium used to cultivate the cells may be any conventional medium suitable for growing the host cell in question and obtaining expression of the  $\alpha$ -amylase variant of the invention. Suitable media are available from commercial suppliers or may be prepared according to published recipes (e.g. as described in catalogues of the American Type Culture Collection).

The  $\alpha$ -amylase variant secreted from the host cells may conveniently be recovered from the culture medium by well-known procedures, including separating the cells from the medium by centrifugation or filtration, and precipitating proteinaceous components of the medium by means of a salt such as ammonium sulphate, followed by the use of chromatographic procedures such as ion exchange chromatography, affinity chromatography, or the like.

### Industrial Applications

The  $\alpha$ -amylase variants of this invention possesses valuable properties allowing for various industrial applications. In particular the enzyme variants finds potential applications as  
5 a component in washing, dishwashing and hard surface cleaning detergent compositions, but it may also be useful in the production of sweeteners and ethanol from starch and for textile desizing. Conditions for conventional starch converting processes and liquefaction and/or saccharification processes  
10 are described in for instance US Patent No. 3,912,590 and EP patent publications Nos. 252,730 and 63,909.

Production of sweeteners from starch: A "traditional" process for conversion of starch to fructose syrups normally consists  
15 of three consecutive enzymatic processes, viz. a liquefaction process followed by a saccharification process and an isomerization process. During the liquefaction process, starch is degraded to dextrins by an  $\alpha$ -amylase (e.g. Termamyl™) at pH values between 5.5 and 6.2 and at temperatures of 95-160°C for  
20 a period of approx. 2h. In order to ensure an optimal enzyme stability under these conditions, 1mM of calcium is added (40 ppm free calcium ions).

After the liquefaction process the dextrins are converted into  
25 dextrose by addition of a glucoamylase (e.g. AMG™) and a debranching enzyme, such as an isoamylase or a pullulanase (e.g. Promozyme™). Before this step the pH is reduced to a value below 4.5, maintaining the high temperature (above 95°C), and the liquefying  $\alpha$ -amylase activity is denatured. The tem-  
30 perature is lowered to 60°C, and glucoamylase and debranching enzyme are added. The saccharification process proceeds for 24-72 hours.

After the saccharification process the pH is increased to a  
35 value in the range of 6-8, preferably pH 7.5, and the calcium is removed by ion exchange. The dextrose syrup is then converted into high fructose syrup using, e.g., an immobilized glucoseisomerase (such as Sweetzyme™).

At least 3 enzymatic improvements of this process could be obtained. All three improvements could be seen as individual benefits, but any combination (e.g. 1+2, 1+3, 2+3 or 1+2+3) could be employed:

5

Improvement 1. Reduction of the calcium dependency of the liquefying  $\alpha$ -amylase.

Addition of free calcium is required to ensure adequately high  
10 stability of the  $\alpha$ -amylase, but free calcium strongly inhibits the activity of the glucoseisomerase and needs to be removed, by means of an expensive unit operation, to an extent which reduces the level of free calcium to below 3-5 ppm. Cost savings could be obtained if such an operation could be avoided  
15 and the liquefaction process could be performed without addition of free calcium ions.

To achieve that, a less calcium-dependent Termamyl-like  $\alpha$ -amylase which is stable and highly active at low  
20 concentrations of free calcium (< 40 ppm) is required. Such a Termamyl-like  $\alpha$ -amylase should have a pH optimum at a pH in the range of 4.5-6.5, preferably in the range of 4.5-5.5.

Improvement 2. Reduction of formation of unwanted Maillard  
25 products

The extent of formation of unwanted Maillard products during the liquefaction process is dependent on the pH. Low pH favours reduced formation of Maillard products. It would thus be  
30 desirable to be able to lower the process pH from around pH 6.0 to a value around pH 4.5; unfortunately, all commonly known, thermostable Termamyl-like  $\alpha$ -amylases are not very stable at low pH (i.e. pH < 6.0) and their specific activity is generally low.

35

Achievement of the above-mentioned goal requires a Termamyl-like  $\alpha$ -amylase which is stable at low pH in the range of

4.5-5.5 and at free calcium concentrations in the range of 0-40 ppm, and which maintains a high specific activity.

### Improvement 3.

- 5 It has been reported previously (US patent 5,234,823) that when saccharifying with *A. niger* glucoamylase and *B. acidopullulyticus* pullulanase, the presence of residual  $\alpha$ -amylase activity from the liquefaction process can lead to lower yields of
- 10 dextrose if the  $\alpha$ -amylase is not inactivated before the saccharification stage. This inactivation can typically be carried out by adjusting the pH to below 4.3 at 95°C, before lowering the temperature to 60°C for saccharification.
- 15 The reason for this negative effect on dextrose yield is not fully understood, but it is assumed that the liquefying  $\alpha$ -amylase (for example Termamyl™ 120 L from *B. licheniformis*) generates "limit dextrans" (which are poor substrates for *B. acidopullulyticus* pullulanase) by hydrolysing 1,4-alpha-
- 20 glucosidic linkages close to and on both sides of the branching points in amylopectin. Hydrolysis of these limit dextrans by glucoamylase leads to a build-up of the trisaccharide panose, which is only slowly hydrolysed by glucoamylase.
- 25 The development of a thermostable  $\alpha$ -amylase which does not suffer from this disadvantage would be a significant process improvement, as no separate inactivation step would be required.
- 30 If a Termamyl-like, low-pH-stable  $\alpha$ -amylase is developed, an alteration of the specificity could be an advantage needed in combination with increased stability at low pH.
- The methodology and principles of the present invention make it
- 35 possible to design and produce variants according to the invention having the required properties as outlined above.

### Detergent Compositions

According to the invention, the  $\alpha$ -amylase may typically be a component of a detergent composition. As such, it may be included in the detergent composition in the form of a non-dusting granulate, a stabilized liquid, or a protected enzyme.

5 Non-dusting granulates may be produced, e.g. as disclosed in US 4,106,991 and 4,661,452 (both to Novo Industri A/S) and may optionally be coated by methods known in the art. Examples of waxy coating materials are poly(ethylene oxide) products (polyethyleneglycol, PEG) with mean molar weights of 1000 to

10 20000, ethoxylated nonylphenols having from 16 to 50 ethylene oxide units; ethoxylated fatty alcohols in which the alcohol contains from 12 to 20 carbon atoms and in which there are 15 to 80 ethylene oxide units; fatty alcohols; fatty acids; and mono- and di- and triglycerides of fatty acids. Examples of

15 film-forming coating materials suitable for application by fluid bed techniques are given in patent GB 1483591. Liquid enzyme preparations may, for instance, be stabilized by adding a polyol such as propylene glycol, a sugar or sugar alcohol, lactic acid or boric acid according to established methods.

20 Other enzyme stabilizers are well known in the art. Protected enzymes may be prepared according to the method disclosed in EP 238,216.

The detergent composition of the invention may be in any convenient form, e.g. as powder, granules, paste or liquid. A

25 liquid detergent may be aqueous, typically containing up to 70% of water and 0-30% of organic solvent, or nonaqueous.

The detergent composition comprises one or more surfactants, each of which may be anionic, nonionic, cationic, or zwitter-

30 ionic. The detergent will usually contain 0-50% of anionic surfactant such as linear alkylbenzenesulfonate (LAS), alpha-olefinsulfonate (AOS), alkyl sulfate (fatty alcohol sulfate) (AS), alcohol ethoxysulfate (AEOS or AES), secondary alkane-sulfonates (SAS), alpha-sulfo fatty acid methyl esters, alkyl-

35 or alkenylsuccinic acid or soap. It may also contain 0-40% of nonionic surfactant such as alcohol ethoxylate (AEO or AE), carboxylated alcohol ethoxylates, nonylphenol ethoxylate, alkylpolyglycoside, alkyl dimethylamineoxide, ethoxylated fatty

acid monoethanolamide, fatty acid monoethanolamide, or polyhydroxy alkyl fatty acid amide (e.g. as described in WO 92/06154).

- 5 The detergent composition may additionally comprise one or more other enzymes, such as lipase, cutinase, protease, cellulase, peroxidase, e.g., laccase.

The detergent may contain 1-65% of a detergent builder or  
10 complexing agent such as zeolite, diphosphate, triphosphate, phosphonate, citrate, nitrilotriacetic acid (NTA), ethylenediaminetetraacetic acid (EDTA), diethylenetriaminepentaacetic acid (DTMPA), alkyl- or alkenylsuccinic acid, soluble silicates or layered silicates (e.g. SKS-6 from Hoechst). The  
15 detergent may also be unbuilt, i.e. essentially free of detergent builder.

The detergent may comprise one or more polymers. Examples are carboxymethylcellulose (CMC), poly(vinylpyrrolidone) (PVP),  
20 polyethyleneglycol (PEG), poly(vinyl alcohol) (PVA), polycarboxylates such as polyacrylates, maleic/acrylic acid copolymers and lauryl methacrylate/acrylic acid copolymers.

The detergent may contain a bleaching system which may comprise  
25 a  $H_2O_2$  source such as perborate or percarbonate which may be combined with a peracid-forming bleach activator such as tetraacetylenediamine (TAED) or nonanoyloxybenzenesulfonate (NOBS). Alternatively, the bleaching system may comprise peroxy acids of e.g. the amide, imide, or sulfone  
30 type.

The enzymes of the detergent composition of the invention may be stabilized using conventional stabilizing agents, e.g. a polyol such as propylene glycol or glycerol, a sugar or sugar  
35 alcohol, lactic acid, boric acid, or a boric acid derivative as e.g. an aromatic borate ester, and the composition may be formulated as described in e.g. WO 92/19709 and WO 92/19708.

The detergent may also contain other conventional detergent ingredients such as e.g. fabric conditioners including clays, foam boosters, suds suppressors, anti-corrosion agents, soil-suspending agents, anti-soil redeposition agents, dyes, bactericides, optical brighteners, or perfume.

The pH (measured in aqueous solution at use concentration) will usually be neutral or alkaline, e.g. 7-11.

10 Particular forms of detergent compositions within the scope of the invention include:

1) A detergent composition formulated as a granulate having a bulk density of at least 600 g/l comprising

	Linear alkylbenzenesulfonate (calculated as acid)	7	-	12%
20	Alcohol ethoxysulfate (e.g. C <sub>12-18</sub> alcohol, 1-2 EO) or alkyl sulfate (e.g. C <sub>6-18</sub> )	1	-	4%
	Alcohol ethoxylate (e.g. C <sub>14-18</sub> alcohol, 7 EO)	5	-	9%
	Sodium carbonate (as Na <sub>2</sub> CO <sub>3</sub> )	14	-	20%
25	Soluble silicate (as Na <sub>2</sub> O, 2SiO <sub>2</sub> )	2	-	6%
	Zeolite (as NaAlSiO <sub>4</sub> )	15	-	22%
	Sodium sulfate (as Na <sub>2</sub> SO <sub>4</sub> )	0	-	6%
	Sodium citrate/citric acid (as C <sub>6</sub> H <sub>5</sub> NaO <sub>7</sub> /C <sub>6</sub> H <sub>8</sub> O <sub>7</sub> )	0	-	15%
30	Sodium perborate (as NaBO <sub>3</sub> ·H <sub>2</sub> O)	11	-	18%
	TAED	2	-	6%
	Carboxymethylcellulose	0	-	2%
	Polymers (e.g. maleic/acrylic acid copolymer, PVP, PEG)	0	-	3%
35	Enzymes (calculated as pure enzyme protein)	0.0001	-	0.1%
	Minor ingredients (e.g. suds suppressors, perfume, optical brightener, photobleach)	0	-	5%

2) A detergent composition formulated as a granulate having a bulk density of at least 600 g/l comprising

5	Linear alkylbenzenesulfonate (calculated as acid)	6 - 11%
	Alcohol ethoxysulfate (e.g. C <sub>12-18</sub> alcohol, 1-2 EO or alkyl sulfate (e.g. C <sub>16-18</sub> ))	1 - 3%
10	Alcohol ethoxylate (e.g. C <sub>14-15</sub> alcohol, 7 EO)	5 - 9%
	Sodium carbonate (as Na <sub>2</sub> CO <sub>3</sub> )	15 - 21%
	Soluble silicate (as Na <sub>2</sub> O, 2SiO <sub>2</sub> )	1 - 4%
15	Zeolite (as NaAlSiO <sub>4</sub> )	24 - 34%
	Sodium sulfate (as Na <sub>2</sub> SO <sub>4</sub> )	4 - 10%
	Sodium citrate/citric acid (as C <sub>6</sub> H <sub>5</sub> NaO <sub>7</sub> /C <sub>6</sub> H <sub>8</sub> O <sub>7</sub> )	0 - 15%
	Carboxymethylcellulose	0 - 2%
20	Polymers (e.g. maleic/acrylic acid copolymer, PVP, PEG)	1 - 6%
	Enzymes (calculated as pure enzyme protein)	0.0001 - 0.1%
25	Minor ingredients (e.g. suds suppressors, perfume)	0 - 5%

3) A detergent composition formulated as a granulate having a bulk density of at least 600 g/l comprising

30	Linear alkylbenzenesulfonate (calculated as acid)	5 - 9%
	Alcohol ethoxylate (e.g. C <sub>12-15</sub> alcohol, 7 EO)	7 - 14%
35	Soap as fatty acid (e.g. C <sub>16-22</sub> fatty acid)	1 - 3%
	Sodium carbonate (as Na <sub>2</sub> CO <sub>3</sub> )	10 - 17%
	Soluble silicate (as Na <sub>2</sub> O, 2SiO <sub>2</sub> )	3 - 9%
	Zeolite (as NaAlSiO <sub>4</sub> )	23 - 33%
	Sodium sulfate (as Na <sub>2</sub> SO <sub>4</sub> )	0 - 4%
40	Sodium perborate (as NaBO <sub>3</sub> ·H <sub>2</sub> O)	8 - 16%

	TAED	2	-	8%
	Phosphonate (e.g. EDTMPA)	0	-	1%
	Carboxymethylcellulose	0	-	2%
5	Polymers (e.g. maleic/acrylic acid copolymer, PVP, PEG)	0	-	3%
	Enzymes (calculated as pure enzyme protein)	0.0001	-	0.1%
10	Minor ingredients (e.g. suds suppressors, perfume, optical brightener)	0	-	5%

4) A detergent composition formulated as a granulate having a bulk density of at least 600 g/l comprising

15	Linear alkylbenzenesulfonate (calculated as acid)	8	-	12%
	Alcohol ethoxylate (e.g. C <sub>12-15</sub> alcohol, 7 EO)	10	-	25%
20	Sodium carbonate (as Na <sub>2</sub> CO <sub>3</sub> )	14	-	22%
	Soluble silicate (as Na <sub>2</sub> O, 2SiO <sub>2</sub> )	1	-	5%
	Zeolite (as NaAlSiO <sub>4</sub> )	25	-	35%
	Sodium sulfate (as Na <sub>2</sub> SO <sub>4</sub> )	0	-	10%
	Carboxymethylcellulose	0	-	2%
25	Polymers (e.g. maleic/acrylic acid copolymer, PVP, PEG)	1	-	3%
	Enzymes (calculated as pure enzyme protein)	0.0001	-	0.1%
30	Minor ingredients (e.g. suds suppressors, perfume)	0	-	5%

5) An aqueous liquid detergent composition comprising

	Linear alkylbenzenesulfonate (calculated as acid)	15	-	21%
35	Alcohol ethoxylate (e.g. C <sub>12-15</sub> alcohol, 7 EO or C <sub>12-15</sub> alcohol, 5 EO)	12	-	18%
	Soap as fatty acid (e.g. oleic acid)	3	-	13%
40	Alkenylsuccinic acid (C <sub>12-14</sub> )	0	-	13%

	Aminoethanol	8	- 18%
	Citric acid	2	- 8%
	Phosphonate	0	- 3%
	Polymers (e.g. PVP, PEG)	0	- 3%
5	Borate (as $B_2O_3$ )	0	- 2%
	Ethanol	0	- 3%
	Propylene glycol	8	- 14%
	Enzymes (calculated as pure enzyme protein)	0.0001	- 0.1%
10	Minor ingredients (e.g. dispersants, suds suppressors, perfume, optical brightener)	0	- 5%

6) An aqueous structured liquid detergent composition comprising

	Linear alkylbenzenesulfonate (calculated as acid)	15	- 21%
20	Alcohol ethoxylate (e.g. $C_{12-15}$ alcohol, 7 EO, or $C_{12-15}$ alcohol, 5 EO)	3	- 9%
	Soap as fatty acid (e.g. oleic acid)	3	- 10%
	Zeolite (as $NaAlSiO_4$ )	14	- 22%
	Potassium citrate	9	- 18%
25	Borate (as $B_2O_3$ )	0	- 2%
	Carboxymethylcellulose	0	- 2%
	Polymers (e.g. PEG, PVP)	0	- 3%
30	Anchoring polymers such as, e.g., lauryl methacrylate/acrylic acid copolymer; molar ratio 25:1; MW 3800	0	- 3%
	Glycerol	0	- 5%
	Enzymes (calculated as pure enzyme protein)	0.0001	- 0.1%
35	Minor ingredients (e.g. dispersants, suds suppressors, perfume, optical brighteners)	0	- 5%

7) A detergent composition formulated as a granulate having a bulk density of at least 600 g/l comprising

	Fatty alcohol sulfate	5	- 10%
5	Ethoxylated fatty acid monoethanol- amide	3	- 9%
	Soap as fatty acid	0	- 3%
	Sodium carbonate (as $\text{Na}_2\text{CO}_3$ )	5	- 10%
	Soluble silicate (as $\text{Na}_2\text{O}, 2\text{SiO}_2$ )	1	- 4%
	Zeolite (as $\text{NaAlSiO}_4$ )	20	- 40%
10	Sodium sulfate (as $\text{Na}_2\text{SO}_4$ )	2	- 8%
	Sodium perborate (as $\text{NaBO}_3 \cdot \text{H}_2\text{O}$ )	12	- 18%
	TAED	2	- 7%
	Polymers (e.g. maleic/acrylic acid copolymer, PEG)	1	- 5%
15	Enzymes (calculated as pure enzyme protein)	0.0001	- 0.1%
	Minor ingredients (e.g. optical brightener, suds suppressors, per- fume)	0	- 5%

8) A detergent composition formulated as a granulate comprising

	Linear alkylbenzenesulfonate (calculated as acid)	8	- 14%
25	Ethoxylated fatty acid monoethanol- amide	5	- 11%
	Soap as fatty acid	0	- 3%
	Sodium carbonate (as $\text{Na}_2\text{CO}_3$ )	4	- 10%
	Soluble silicate (as $\text{Na}_2\text{O}, 2\text{SiO}_2$ )	1	- 4%
	Zeolite (as $\text{NaAlSiO}_4$ )	30	- 50%
30	Sodium sulfate (as $\text{Na}_2\text{SO}_4$ )	3	- 11%
	Sodium citrate (as $\text{C}_6\text{H}_5\text{NaO}_7$ )	5	- 12%
	Polymers (e.g. PVP, maleic/acrylic acid copolymer, PEG)	1	- 5%
35	Enzymes (calculated as pure enzyme protein)	0.0001	- 0.1%
	Minor ingredients (e.g. suds suppressors, perfume)	0	- 5%

9) A detergent composition formulated as a granulate comprising

	Linear alkylbenzenesulfonate (calculated as acid)	6	- 12%
	Nonionic surfactant	1	- 4%
5	Soap as fatty acid	2	- 6%
	Sodium carbonate (as $\text{Na}_2\text{CO}_3$ )	14	- 22%
	Zeolite (as $\text{NaAlSiO}_3$ )	18	- 32%
	Sodium sulfate (as $\text{Na}_2\text{SO}_4$ )	5	- 20%
	Sodium citrate (as $\text{C}_6\text{H}_5\text{Na}_3\text{O}_7$ )	3	- 8%
10	Sodium perborate (as $\text{NaBO}_3 \cdot \text{H}_2\text{O}$ )	4	- 9%
	Bleach activator (e.g. NOBS or TAED)	1	- 5%
	Carboxymethylcellulose	0	- 2%
15	Polymers (e.g. polycarboxylate or PEG)	1	- 5%
	Enzymes (calculated as pure enzyme protein)	0.0001	- 0.1%
	Minor ingredients (e.g. optical brightener, perfume)	0	- 5%

10) An aqueous liquid detergent composition comprising

	Linear alkylbenzenesulfonate (calculated as acid)	15	- 23%
25	Alcohol ethoxysulfate (e.g. $\text{C}_{12-15}$ alcohol, 2-3 EO)	8	- 15%
	Alcohol ethoxylate (e.g. $\text{C}_{12-15}$ al- cohol, 7 EO, or $\text{C}_{12-15}$ alcohol, 5 EO)	3	- 9%
30	Soap as fatty acid (e.g. lauric acid)	0	- 3%
	Aminoethanol	1	- 5%
	Sodium citrate	5	- 10%
	Hydrotrope (e.g. sodium toluenesulfonate)	2	- 6%
35	Borate (as $\text{B}_4\text{O}_7$ )	0	- 2%
	Carboxymethylcellulose	0	- 1%
	Ethanol	1	- 3%
	Propylene glycol	2	- 5%

	Enzymes (calculated as pure enzyme protein)	0.0001 - 0.1%
5	Minor ingredients (e.g. polymers, dispersants, perfume, optical brighteners)	0 - 5%

11) An aqueous liquid detergent composition comprising

	Linear alkylbenzenesulfonate (calculated as acid)	20 - 32%
10	Alcohol ethoxylate (e.g. C <sub>12-15</sub> alcohol, 7 EO, or C <sub>12-15</sub> alcohol, 5 EO)	6 - 12%
	Aminoethanol	2 - 6%
	Citric acid	8 - 14%
15	Borate (as B <sub>2</sub> O <sub>3</sub> )	1 - 3%
	Polymer (e.g. maleic/acrylic acid copolymer, anchoring polymer such as, e.g., lauryl methacrylate/acrylic acid copolymer)	0 - 3%
20	Glycerol	3 - 8%
	Enzymes (calculated as pure enzyme protein)	0.0001 - 0.1%
25	Minor ingredients (e.g. hydro-tropes, dispersants, perfume, optical brighteners)	0 - 5%

12) A detergent composition formulated as a granulate having a bulk density of at least 600 g/l comprising

30	Anionic surfactant (linear alkylbenzenesulfonate, alkyl sulfate, alpha-olefinsulfonate, alpha-sulfo fatty acid methyl esters, alkanesulfonates, soap)	25 - 40%
35	Nonionic surfactant (e.g. alcohol ethoxylate)	1 - 10%
	Sodium carbonate (as Na <sub>2</sub> CO <sub>3</sub> )	8 - 25%
	Soluble silicates (as Na <sub>2</sub> O, 2SiO <sub>2</sub> )	5 - 15%
	Sodium sulfate (as Na <sub>2</sub> SO <sub>4</sub> )	0 - 5%
40	Zeolite (as NaAlSiO <sub>4</sub> )	15 - 28%
	Sodium perborate (as NaBO <sub>3</sub> ·4H <sub>2</sub> O)	0 - 20%

	Bleach activator (TAED or NOBS)	0	-	5%
	Enzymes (calculated as pure enzyme protein)	0.0001	-	0.1%
5	Minor ingredients (e.g. perfume, optical brighteners)	0	-	3%

13) Detergent formulations as described in 1) - 12) wherein all or part of the linear alkylbenzenesulfonate is replaced by (C<sub>12</sub>-C<sub>18</sub>) alkyl sulfate.

10

14) A detergent composition formulated as a granulate having a bulk density of at least 600 g/l comprising

	(C <sub>12</sub> -C <sub>18</sub> ) alkyl sulfate	9	-	15%
15	Alcohol ethoxylate	3	-	6%
	Polyhydroxy alkyl fatty acid amide	1	-	5%
	Zeolite (as NaAlSiO <sub>4</sub> )	10	-	20%
	Layered disilicate (e.g. SK56 from Hoechst)	10	-	20%
20	Sodium carbonate (as Na <sub>2</sub> CO <sub>3</sub> )	3	-	12%
	Soluble silicate (as Na <sub>2</sub> O, 2SiO <sub>2</sub> )	0	-	6%
	Sodium citrate	4	-	8%
	Sodium percarbonate	13	-	22%
	TAED	3	-	8%
25	Polymers (e.g. polycarboxylates and PVP=	0	-	5%
	Enzymes (calculated as pure enzyme protein)	0.0001	-	0.1%
30	Minor ingredients (e.g. optical brightener, photo bleach, perfume, suds suppressors)	0	-	5%

15) A detergent composition formulated as a granulate having a bulk density of at least 600 g/l comprising

(C <sub>12</sub> -C <sub>18</sub> ) alkyl sulfate	4	-	8%
Alcohol ethoxylate	11	-	15%

## SUBSTITUTE SHEET (RULE 26)

	Soap	1	-	4%
	Zeolite MAP or zeolite A	35	-	45%
	Sodium carbonate (as $\text{Na}_2\text{CO}_3$ )	2	-	8%
	Soluble silicate (as $\text{Na}_2\text{O}, 2\text{SiO}_2$ )	0	-	4%
5	Sodium percarbonate	13	-	22%
	TAED	1	-	8%
	Carboxymethyl cellulose	0	-	3%
	Polymers (e.g. polycarboxylates and PVP)	0	-	3%
10	Enzymes (calculated as pure enzyme protein)	0.0001	-	0.1%
	Minor ingredients (e.g. optical brightener, phosphonate, perfume)	0	-	3%

15 16) Detergent formulations as described in 1) - 15) which contain a stabilized or encapsulated peracid, either as an additional component or as a substitute for already specified bleach systems.

20 17) Detergent compositions as described in 1), 3), 7), 9) and 12) wherein perborate is replaced by percarbonate.

18) Detergent compositions as described in 1), 3), 7), 9), 12), 14) and 15) which additionally contain a manganese catalyst.

25 The manganese catalyst may, e.g., be one of the compounds described in "Efficient manganese catalysts for low-temperature bleaching", Nature 369, 1994, pp. 637-639.

19) Detergent composition formulated as a nonaqueous detergent  
30 liquid comprising a liquid nonionic surfactant such as, e.g., linear alkoxylated primary alcohol, a builder system (e.g. phosphate), enzyme and alkali. The detergent may also comprise anionic surfactant and/or a bleach system.

35 The  $\alpha$ -amylase variant of the invention may be incorporated in concentrations conventionally employed in detergents. It is at present contemplated that, in the detergent composition of the invention, the  $\alpha$ -amylase may be added in an amount correspon-

ding to 0.00001-1 mg (calculated as pure enzyme protein) of  $\alpha$ -amylase per liter of wash liquor.

#### Dishwashing Composition

- 5 The dishwashing detergent composition comprises a surfactant which may be anionic, non-ionic, cationic, amphoteric or a mixture of these types. The detergent will contain 0-90% of non-ionic surfactant such as low- to non-foaming ethoxylated propoxylated straight-chain alcohols.
- 10 The detergent composition may contain detergent builder salts of inorganic and/or organic types. The detergent builders may be subdivided into phosphorus-containing and non-phosphorus-containing types. The detergent composition usually contains 1-90% of detergent builders.
- 15 Examples of phosphorus-containing inorganic alkaline detergent builders, when present, include the water-soluble salts especially alkali metal pyrophosphates, orthophosphates, and polyphosphates. An example of phosphorus-containing organic alkaline detergent builder, when present, includes the water-
- 20 soluble salts of phosphonates. Examples of non-phosphorus-containing inorganic builders, when present, include water-soluble alkali metal carbonates, borates and silicates as well as the various types of water-insoluble crystalline or amorphous aluminosilicates of which zeolites are the best-known
- 25 representatives.

Examples of suitable organic builders include the alkali metal, ammonium and substituted ammonium, citrates, succinates, malonates, fatty acid sulphonates, carboxymethoxy succinates,

- 30 ammonium polyacetates, carboxylates, polycarboxylates, aminopolycarboxylates, polyacetyl carboxylates and polyhydroxysulphonates.

Other suitable organic builders include the higher molecular

- 35 weight polymers and co-polymers known to have builder properties, for example appropriate polyacrylic acid, polymaleic acid and polyacrylic/polymaleic acid copolymers and their salts.

The dishwashing detergent composition may contain bleaching agents of the chlorine/bromine-type or the oxygen-type. Examples of inorganic chlorine/bromine-type bleaches are lithium, sodium or calcium hypochlorite and hypobromite as well as chlorinated trisodium phosphate. Examples of organic chlorine/bromine-type bleaches are heterocyclic N-bromo and N-chloro imides such as trichloroisocyanuric, tribromoisocyanuric, dibromoisocyanuric and dichloroisocyanuric acids, and salts thereof with water-solubilizing cations such as potassium and sodium. Hydantoin compounds are also suitable.

The oxygen bleaches are preferred, for example in the form of an inorganic persalt, preferably with a bleach precursor or as a peroxy acid compound. Typical examples of suitable peroxy bleach compounds are alkali metal perborates, both tetrahydrates and monohydrates, alkali metal percarbonates, persilicates and perphosphates. Preferred activator materials are TAED and glycerol triacetate.

The dishwashing detergent composition of the invention may be stabilized using conventional stabilizing agents for the enzyme(s), e.g. a polyol such as e.g. propylene glycol, a sugar or a sugar alcohol, lactic acid, boric acid, or a boric acid derivative, e.g. an aromatic borate ester.

The dishwashing detergent composition of the invention may also contain other conventional detergent ingredients, e.g. deflocculant material, filler material, foam depressors, anti-corrosion agents, soil-suspending agents, sequestering agents, anti-soil redeposition agents, dehydrating agents, dyes, bactericides, fluorescers, thickeners and perfumes.

Finally, the  $\alpha$ -amylase variant of the invention may be used in conventional dishwashing detergents, e.g. in any of the detergents described in any of the following patent publications:

EP 518719, EP 518720, EP 518721, EP 516553, EP 516554,

EP 516555, GB 2200132, DE 3741617, DE 3727911, DE 4212166,  
DE 4137470, DE 3833047, WO 93/17089, DE 4205071, WO 52/09680,  
WO 93/18129, WO 93/04153, WO 92/06157, WO 92/08777, EP 429124,  
WO 93/21299, US 5141664, EP 561452, EP 561446, GB 2234980,  
5 WO 93/03129, EP 481547, EP 530870, EP 533239, EP 554943,  
EP 346137, US 5112518, EP 318204, EP 318279, EP 271155,  
EP 271156, EP 346136, GB 2228945, CA 2006687, WO 93/25651,  
EP 530635, EP 414197, US 5240632.

# 10 EXAMPLES

## EXAMPLE 1

### 15 Example on Homology building of TERM

The overall homology of the *B. licheniformis*  $\alpha$ -amylase (in the following referred to as TERM) to other Termamyl-like  $\alpha$ -amylases is high and the percent similarity is extremely high.  
20 The similarity calculated for TERM to BSG (the *B. stearothermophilus*  $\alpha$ -amylase with SEQ ID NO 6), and BAN (the *B. amyloliquefaciens*  $\alpha$ -amylase with SEQ ID NO 4) using the University of Wisconsin Genetics Computer Group's program GCG gave 89% and 78%, respectively. TERM has a deletion of 2  
25 residues between residue G180 and K181 compared to BAN and BSG. BSG has a deletion of 3 residues between G371 and I372 in comparison with BAN and TERM. Further BSG has a C-terminal extension of more than 20 residues compared to BAN and TERM. BAN has 2 residues less and TERM has one residue less in the  
30 N-terminal compared to BSG.

The structure of the *B. licheniformis* (TERM) and of the *B. amyloliquefaciens*  $\alpha$ -amylase (BAN), respectively, was model built on the structure disclosed in Appendix 1 herein. The  
35 structure of other Termamyl-like  $\alpha$ -amylases (e.g. those disclosed herein) may be built analogously.

In comparison with the  $\alpha$ -amylase used for elucidating the present structure, TERM differs in that it lacks two residues around 178-182. In order to compensate for this in the model structure, the HOMOLGY program from BIOSYM was used to  
5 substitute the residues in equivalent positions in the structure (not only structurally conserved regions) except for the deletion point. A peptide bond was established between G179(G177) and K180(K180) in TERM(BAN). The close structural relationship between the solved structure and the model  
10 structure (and thus the validity of the latter) is indicated by the presence of only very few atoms found to be too close together in the model.

To this very rough structure of TERM was then added all waters  
15 (605) and ions (4 Calcium and 1 Sodium) from the solved structure (Appendix 1) at the same coordinates as for said solved structure using the INSIGHT program. This could be done with only few overlaps - in other words with a very nice fit. This model structure were then minimized using 200 steps of  
20 Steepest descent and 600 steps of Conjugated gradient (see Brooks et al 1983, J. Computational Chemistry 4, p.187-217). The minimized structure was then subjected to molecular dynamics, 5ps heating followed by up to 200ps equilibration but more than 35ps. The dynamics as run with the Verlet algorithm  
25 and the equilibration temperature 300K were kept using the Berendsen coupling to a waterbath (Berendsen et. al., 1984, J. Chemical Physics 81, p. 3684-3690). Rotations and translations were removed every picosecond. The potential energy became stable after appr. 35ps equilibration. A mean dynamics structure was extracted and can be used for further analysis.  
30

#### EXAMPLE 2

Determination of residues within 10Å from the ions present in  
35 the solved structure

The coordinates of Appendix 1 are read into the INSIGHT program provided by BIOSYM technologies. The spatial coordinates are

presented showing the bonds between the atoms. The ions are presented as well as the water atoms. The program package part of creating subset are used to create a 10Å subset around the Calcium and the Sodium ions in the structure using the command  
5 ZONE. All residues having an atom within the 10Å are compiled and written out by the LIST MOLECULE command. By giving the ions the name ium in the coordinate file a 10Å sphere around all atoms called ium is compiled. The specific residues identified in this manner are given further above in the  
10 section entitled "Ca<sup>2+</sup> dependency".

### EXAMPLE 3

#### Determination of cavities in the solved structure (Appendix 1)

15 The solved structure exhibits many internal holes and cavities. When analysing for such cavities the Connolly program is normally used (Lee, B. and Richards, F.M. (1971) J. Mol. Biol. 55,p. 379-400). The program uses a probe with radius to search  
20 the external and internal surface of the protein. The smallest hole observable in this way has the probe radius.

To analyse the solved structure a modified version of the Connolly program included in the program of INSIGHT were used.  
25 First the water molecules and the ions were removed by unmerging these atoms from the solved structure. By using the command MOLECULE SURFACE SOLVENT the solvent accessible surface area were calculated for all atoms and residues using a probe radius of 1.4Å, and displayed on the graphics screen together  
30 with the model of the solved structure. The internal cavities where then seen as dot surfaces with no connections to external surface.

Mutant suggestions for filling out the holes are given in the  
35 specification (in the section entitled "Variants with increased thermostability and/or altered temperature optimum"). By using the homology build structures or/and the sequence alignment

mutations for the homologous structures of TERM and BSG and BAN can be made.

#### EXAMPLE 4

5

Construction of Termamyl™ variants in accordance with the invention

Termamyl (SEQ ID NO. 2) is expressed in *B. subtilis* from a  
10 plasmid denoted pDN1528. This plasmid contains the complete  
gene encoding Termamyl, *amyL*, the expression of which is  
directed by its own promoter. Further, the plasmid contains the  
origin of replication, *ori*, from plasmid pUB110 and the *cat*  
gene from plasmid pC194 conferring resistance towards  
15 chloramphenicol. pDN1528 is shown in Fig. 9.

A specific mutagenesis vector containing a major part of the  
coding region of SEQ ID NO 1 was prepared. The important  
features of this vector, denoted pJeEN1, include an origin of  
20 replication derived from the pUC plasmids, the *cat* gene  
conferring resistance towards chloramphenicol, and a  
frameshift-containing version of the *bla* gene, the wild type of  
which normally confers resistance towards ampicillin (*amp<sup>r</sup>*  
phenotype). This mutated version results in an *amp<sup>s</sup>* phenotype.  
25 The plasmid pJeEN1 is shown in Fig. 10, and the *E. coli* origin  
of replication, *ori*, *bla*, *cat*, the 5'-truncated version of the  
Termamyl *amylase* gene, and selected restriction sites are  
indicated on the plasmid.

30 Mutations are introduced in *amyL* by the method described by  
Deng and Nickoloff (1992, Anal. Biochem. 200, pp. 81-88) except  
that plasmids with the "selection primer" (primer #6616; see  
below) incorporated are selected based on the *amp<sup>r</sup>* phenotype of  
transformed *E. coli* cells harboring a plasmid with a repaired  
35 *bla* gene, instead of employing the selection by restriction  
enzyme digestion outlined by Deng and Nickoloff. Chemicals and  
enzymes used for the mutagenesis were obtained from the

Chameleon™ mutagenesis kit from Stratagene (catalogue number 200509).

After verification of the DNA sequence in variant plasmids, the truncated gene, containing the desired alteration, is subcloned into pDN1528 as a *Pst*I-*Eco*RI fragment and transformed into a protease- and amylase-depleted *Bacillus subtilis* strain in order to express the variant enzyme.

- 10 The Termamyl variant V54W was constructed by the use of the following mutagenesis primer (written 5' to 3', left to right):

PG GTC GTA GGC ACC GTA GCC CCA ATC CGC TTG

- 15 The Termamyl variant A52W + V54W was constructed by the use of the following mutagenesis primer (written 5' to 3', left to right):

PG GTC GTA GGC ACC GTA GCC CCA ATC CCA TTG GCT CG

20

Primer #6616 (written 5' to 3', left to right; P denotes a 5' phosphate):

P CTG TGA CTG GTG AGT ACT CAA CCA AGT C

25

#### EXAMPLE 5

**Saccharification in the presence of "residual"  $\alpha$ -amylase activity**

30

Two appropriate Termamyl variants with altered specificity were evaluated by saccharifying a DE 10 (DE = dextrose equivalent) maltodextrin substrate with *A. niger* glucoamylase and *B. acidopullulyticus* pullulanase under conditions where the variant amylase was active.

Saccharification: Substrates for saccharification were prepared by dissolving 230 g DE 10 spray-dried maltodextrin, prepared

from common corn starch, in 460 ml boiling deionized water and adjusting the dry substance (DS) content to approximately 30% w/w. The pH was adjusted to 4.7 (measured at 60°C) and aliquots of substrate corresponding to 15 g dry weight were transferred to 50 ml blue cap glass flasks.

The flasks were then placed in a shaking water bath equilibrated at 60°C, and the enzymes added. The pH was readjusted to 4.7 where necessary.

The following enzymes were used:

Glucoamylase: AMG™ (Novo Nordisk A/S); dosage 0.18 AG/g DS  
 Pullulanase: Promozyme™ (Novo Nordisk A/S);  
 dosage 0.06 PUN/g DS  
 $\alpha$ -Amylases: Termamyl™ (Novo Nordisk A/S); dosage 60 NU/g DS  
 Termamyl variant V54W; dosage 60 NU/g DS  
 Termamyl variant V54W + A52W; dosage 60 NU/g DS

2 ml samples were taken periodically. The pH of each sample was adjusted to about 3.0, and the sample was then heated in a boiling water bath for 15 minutes to inactivate the enzymes. After cooling, the samples were treated with approximately 0.1 g mixed-bed ion exchange resin (BIO-Rad 501-X (D)) for 30 minutes on a rotary mixer and then filtered. The carbohydrate composition of each sample was determined by HPLC. The following results were obtained after 72 hours [DP<sub>n</sub> denotes a dextrose (D-glucose) oligomer with n glucose units]:

$\alpha$ -amylase	%DP <sub>1</sub>	%DP <sub>2</sub>	%DP <sub>3</sub>	%DP <sub>4</sub>
None (control)	95.9	2.8	0.4	1.0
V54W	96.0	2.9	0.4	0.8
V54W + A52W	95.9	2.8	0.4	0.8
Termamyl™	95.6	2.8	0.8	0.8

It can be seen from the above results that compared with the control (no  $\alpha$ -amylase activity present during liquefaction), the presence of  $\alpha$ -amylase activity from variants V54W and V54W + A52W did not lead to elevated panose (DP<sub>1</sub>) levels. In contrast, Termamyl  $\alpha$ -amylase activity resulted in higher levels of panose and a subsequent loss of D-glucose (DP<sub>1</sub>) yield.

Thus, if  $\alpha$ -amylase variants V54W or V54W + A52W are used for starch liquefaction, it will not be necessary to inactivate the residual  $\alpha$ -amylase activity before the commencement of saccharification.

#### EXAMPLE 6

#### 15 Calcium-binding affinity of $\alpha$ -amylase variants of the invention

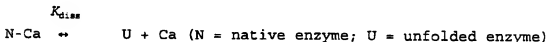
Unfolding of amylases by exposure to heat or to denaturants such as guanidine hydrochloride is accompanied by a decrease in fluorescence. Loss of calcium ions leads to unfolding, and the affinity of  $\alpha$ -amylases for calcium can be measured by fluorescence measurements before and after incubation of each  $\alpha$ -amylase (e.g. at a concentration of 10  $\mu$ g/ml) in a buffer (e.g. 50 mM HEPES, pH 7) with different concentrations of calcium (e.g. in the range of 1  $\mu$ M-100 mM) or of EGTA (e.g. in the range of 1-1000  $\mu$ M) [EGTA = 1,2-di(2-aminoethoxy)ethane-25 *N,N,N',N'*-tetraacetic acid] for a sufficiently long period of time (such as 22 hours at 55°C).

The measured fluorescence  $F$  is composed of contributions from the folded and unfolded forms of the enzyme. The following equation can be derived to describe the dependence of  $F$  on calcium concentration ( $[Ca]$ ):

$$F = [Ca] / (K_{diss} + [Ca]) (\alpha_N - \beta_N \log([Ca])) + K_{diss} / (K_{diss} + [Ca]) (\alpha_U - \beta_U \log([Ca]))$$

where  $\alpha_N$  is the fluorescence of the native (folded) form of the enzyme,  $\beta_N$  is the linear dependence of  $\alpha_N$  on the logarithm of

the calcium concentration (as observed experimentally),  $\alpha_0$  is the fluorescence of the unfolded form and  $\beta_0$  is the linear dependence of  $\alpha_0$  on the logarithm of the calcium concentration.  $K_{d,ss}$  is the apparent calcium-binding constant for an equilibrium process as follows:



- 10 In fact, unfolding proceeds extremely slowly and is irreversible. The rate of unfolding is a dependent on calcium concentration, and the dependency for a given  $\alpha$ -amylase provides a measure of the Ca-binding affinity of the enzyme. By defining a standard set of reaction conditions (e.g. 22 hours
- 15 at 55°C), a meaningful comparison of  $K_{d,ss}$  for different  $\alpha$ -amylases can be made. The calcium dissociation curves for  $\alpha$ -amylases in general can be fitted to the equation above, allowing determination of the corresponding values of  $K_{d,ss}$ .
- 20 The following values for  $K_{d,ss}$  were obtained for a parent Termamyl-like  $\alpha$ -amylase having the amino acid sequence shown in SEQ ID No. 1 of WO 95/26397 and for the indicated variant thereof according to the invention:

25 $\alpha$ -Amylase	$K_{d,ss}$ (mol/l)
L351C + M430C + T183* + G184*	$1.7 (\pm 0.5) \times 10^{-3}$
Parent	$3.5 (\pm 1.1) \times 10^{-1}$

- 30 It is apparent from the above that the calcium-binding affinity of the variant in question binds calcium significantly more strongly than the parent, and thereby has a correspondingly lower calcium dependency than the parent.

35

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## SEQUENCE LISTING

In the following SEQ ID Nos. 1, 3, 5 the 5', coding sequence and 3' sequence of the relevant  $\alpha$ -amylase genes are illustrated. The 5' sequence is the first separate part of the sequence written with lower case letters, the coding sequence is the intermediate part of the sequence, where the signal sequence is written with lower case letters and the sequence encoding the mature  $\alpha$ -amylase is written with upper case letters, and the 3' sequence is the third separate part of the sequence written with lower case letters.

## SEQ ID No. 1

15 cggaagattggaagtacaaaaataagcaaaagattgtcaatcatgtcatgagccatcggg-  
gagacggaaaaatcgtctta atgcacgatatttatgcaacgttcgcagatgctgctgaa-  
gagattattaaaaagctgaaagcaaaaggctatcaattggt aactgtatctcagcttga-  
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20 ttttggagaataatatagggaaaatggtacttgttaaaaattcggaatatttatacaacatc-  
atatgtttcacattgaaa ggggaggagaatc

atgaacaacaaaaacggctttacgcccgatgtgtagcgtgttatttgcgctcatcttctt-  
gctgc ctcatctctgcagcagcgcgGCAAATCTTAATGGGACGCTGATGCAGTATTTT-  
25 GAATGGTACATGCCAATGACGGCCAA CATTGGAGGCGTTTGCAAAACGACTCGGCATAT-  
TTGGCTGAACACGGTATTACTGCCGTCTGGATTCCCCGGCATATAA GGGAAACGAGC-  
CAAGCGGATGTGGGCTACGGTGCTTACGACCTTTATGATTAGGGGAGTTTCATCAAAAG-  
GGACGGTTC GGACAAAGTACGGCACAAAAGGAGAGCTGCAATCTGCGATCAAAAGTCTTC-  
ATTCGCCGACATTAACGTTTACGGGGAT GTGGTCATCAACCACAAAGCGCGCTGA-  
30 TGCACCGAAGATGTAAACCGCGTTGAAGTCGATCCCGCTGACCGCAACCG CGTAATTT-  
CAGGAGAACACCTAATTAAAGCCTGGACACATTTTCAATTTTCCGGGGCGCGGCAGCACATA-  
CAGCGATTTTA AATGGCATTGGTACCATTTTGACGGAACCGATTGGGACGAGTCCCGAAA-  
GCTGAACCGCATCTATAAGTTTCAAGGAAAG GCTTGGGATTGGGAAGTTTCCAATGAA-  
AACGGCAACTATGATTATTGTATGTATGCCGACATCGATTATGACCATCCTGA TGTCGACG-  
35 CAGAAATTAAGAGATGGGGCACTTGGTATGCCAATGAACTGCAATTGGACGGTTTCCGTCTT-  
GATGCTGTCA AACACATTAAATTTTCTTTTTTGCGGGATTGGGTTAATCATGTACAGGGA-  
AAAAACGGGGGAAGGAAATGTTTACGGTAGCT GAATATTGGCAGAAT-  
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GTGCC GCTTCATTATCAGTTCCATGCTGCATCGACACAGGGAGGCGGCTATGATATGAG-  
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 ATAACCATGATACACAGCCGGGGCAATCGCTTGAGTCGACTGTCCAA ACATGGTTTAAG-  
 CCGCTTGCTTACGCTTTTATTCTCACAAAGGAATCTGGATACCCTCAGGTTTTCTACGGG-  
 5 GATATGTA CGGGACGAAAGGAGACTCCCAGCGCGAAATTCCTGCCTTGAAACACAAAAT-  
 TGAACCGATCTTAAAGAGCGAGAAAACAGT ATGCGTACGGAGCACAGCATGATTATTTCGAC-  
 CACCATGACATTGTCGGCTGGACAAGGGAAGGCGACGCTCGGTTGCA AATTGAGTTTGG-  
 CGGCATTAATAACAGACGGACCCGGTGGGGCAAAGCGAATGTATGTGCGGCCGGCA-  
 AAACGCCGGTGA GACATGGCATGACATTACCGGAAACCGTTCGGAGCCGGTTGTCATCA-  
 10 ATTCGGAAGGCTGGGGAGAGTTTACGTAAACG GCGGGTCGGTTTCAATTTATGTTCAAA-  
 GATAG

aagagcagagaggacggatttcctgaaggaaatccgttttttttttttt

15 SEQ ID No. 2

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 GELQSAIKSLHSRDINVYGDVIVNHKGGADATEDVTAVEV  
 20 DPADRNRVISGEHLIKAWTHFHFPGRGSTYSDFKWHWHF  
 DGTDWDESRLNRIYKFQKAWDWEVSNENGNIDYLMYAD  
 IDYDHPDVAEIKRWGTWYANELQLDGFRLDAVKHIFKFSF  
 LRDWNVHVREKTKEMFTVAEYWQNDLGALENYLNKTNFN  
 HSVFDVPLHYQFHAASTQGGGYDMRKLNGTVVSKHPLKS  
 25 VTFVDNHDTPQGSLESTVQTFKPLAYAFILTRESGYPQ  
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 VQR

30

SEQ ID No. 3

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 35 ctgaagaagtggatcgattg tttagagaaaagaagaccataaaaaatccttgcctgt-  
 catcagacagggatattttttatgctgtccagactgtccgct gtgtaaaaataagggaata-  
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5 CCAATCCGATAACGATACGGACCTTATGATTGTATGATTAGGAGAATTCAGCAAAA-  
AGGGACGGTCAGAAC GAAATACGGCACAAAATCAGAGCTTCAAGATGCGATCGGCTCAC-  
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10 ACGTACAGTGATTTTAAATG GCATTGGTATCATTTCGACGGAGCGGACTGGGATGAATCCC-  
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TATCCGTATTGATGCCG CAAACATATTAAATTTTCATTCTGCGTGATTGGGTTCCAGG-  
15 CCGTCAGACAGCGGCACGGGAAAAGAAATGTTTACGGTTG CCGAGTATTGGCAG-  
AATAATGCCGGAAACTCGAAAACACTTGAATAAAACAAGCTTTAATCAATCCGTGTTT-  
GATGTT CCGCTTCATTTCATTTACAGGCGGCTTCCTCACAAGGAGGCGGATATGATAT-  
GAGGCGTTTGCTGGACGGTACCGTTGT GTCCAGGCATCCGAAAAGGCGGTTACATTGTG-  
TGAAAATCATGACACAGCCGGGACAGTCATTGGAATCGACAGTCC AAAGTTGGTTAA-  
20 ACCGCTTGATACGCCCTTTATTTTGACAAGAGAATCCGGTTATCCTCAGGTGTTCTATGGG-  
GATATG TACGGGACAAAAGGGACATCGCCAAAGGAAATCCCTCACTGAAAGATAATATA-  
GAGCCGATTTTAAAGCGCGTAAGGA GTACGCATACGGGCCCCAGCAGCATTTATATTGAC-  
CACCCGGATGTGATCGGATGGACGAGGGAAGGTGACAGCTCCGCC CCAA-  
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25 CCTGAAAAATGCCGGC GAGACATGGTATGACATAACGGGCAACCGTTGAGATAGTAA-  
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30 tttcagcgtatgacaaggtcgccatcaggtgtgacaaatcaggtatgctggctgtcata-  
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caacaggcacggagccgaatctttcgc cttggaaaaataagcggcgatcgtagctgct-  
tccaatatggattgtcatcgggatcgctgcttttaatacacaacgtggg atcc

SEQ ID No. 4

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 5 LQDAIGSLHSRNVQVYGDVVLNHHKAGADATEDVTAVEVNP  
 ANRNQETSEYQIKAWTDFRFPGRGNTYSDFKWHWYHFDG  
 ADWDESRKISRIFKFRGEGKAWDWEVSSSENGNYDYLMYAD  
 VDYDHPDVVAETKKWGIWYANELSLDGFRIDAAKHIKFSF  
 LRDWVQAVRQATGKEMFTVAEYQNNAGKLENYLNKTSFN  
 10 QSVFDVPLHFNLAASSQGGGYDMRRLLDGTVVSRHPEKA  
 VTFVENHDTQPGQSLESTVQTWFKPLAYAFILTRESGYPQ  
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15

SEQ ID No. 5

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 25 TTAACGGCACCATGATGACGATTTTGAATGGTACTTGCCGGATGATGGCAGC TTATGG-  
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 CGCCCGCTTACAA AGGAACAAGCCGCGACGACGTAGGGTACGGAGTATACGACTTGTA-  
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 30 GTGTTGACCCATAAAGCGCGCTGACGGCACGGAATGGGTGGACGCCGTGCAAGTCAAT-  
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 ACGGCGTTGATTGGGACGAAAGCCGAAAAATTGAGCCGCATTACAAAATCCCGCGGCATC  
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 35 GCCGACCTTGATATGGATCA TCCCGAAGTCGTGACCGAGCTGAAAACTGGGGGAAATG-  
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 TCAGTTTTCCTGATTGGTTGTGTCGATGTGCGTTCTCAGACTGSCAAGCCGCTATTTACC  
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GGAACGATGCTTTGTTTGA TGCCCCGTTACACAACAAATTTTATACCGCTTCCAAATCAG-  
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 5 CAGGAAGGATACCCGTCGCTCTTTTATGGTGA CTATTATGGCATTCCACAATATAACAT-  
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 CGGTTTCGGTTTGGGTTCTAGAAAAACGACCGTTTCTACCATCGCTCGGCCGATCAAA-  
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tgccctgcga

15

SEQ ID No. 6

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 20 LWLFPAYKGTSRSDVG YGVYDLYDLGFEFNQKGTVRKYGT  
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 25 FSFFPDWLSYVRSQTGKPLFTVGEYWSYDINKLHNYITKT  
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 30 GKQHAGKVFDLTGNRSDTVTINS DGWGEFKVNGGVSVMV  
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SEQ ID No. 10

35 1 ATPADWRSQS IYFLLTDRFA RTDGSTTATC  
 31 NTADQKYCGG TWQGIIDKLD YIQMGFTAI  
 61 WITPVTAQLP QTTAYGDAYH GYWQQDIYSL  
 91 NENYGTADDL KALSSALHER GMYLMVDVVA

121 NHMGYDGAGS SVDYSVFKEP SSQDYFHFPC  
151 FIQNYEDQIQ VEDCWLGDNT VSLPDLDTTK  
181 DVVKNEWYDW VGSLSVSNYSI DGLRIDTVKH  
211 VQKDFWPGYN KAAGVYCIGE VLDGDPAYTC  
5 241 PYQNVMDGVL NYPIYYPLLN AFKSTSGSMD  
271 DLYNMINTVK SDCPDSTLLG TFVENHDNPR  
301 FASYTNDIAL AKNVAAFIIL NDGIPIIYAG  
331 QEQHYAGGND PANREATWLS GYPTDSELYK  
361 LIASANAIRN YAIKSDTGFV TYKNWPIYKD  
10 391 DITIAMRKGT DGSQIVTILS NKGASGDSYT  
421 LSLSGAGYTA GQQLTEVIGC TTVTVGSDGN  
451 VPVPMAGGLP RVLYPTEKLA GSKICSSS

1	ATH	1	11,902	27,157	32,095	1,00	23,86	6	ATH	54	CG TPR	8	28,238	37,352	24,476	1,00	10,19	6
2	CG1 VAL	1	12,302	27,494	20,658	1,00	24,06	6	ATH	55	CG TPR	8	27,909	38,377	24,371	1,00	10,76	6
3	CG2 VAL	1	10,659	27,948	22,511	1,00	26,37	6	ATH	56	CG1 TPR	8	27,180	37,983	22,222	1,00	11,00	6
4	C VAL	1	13,030	25,096	22,743	1,00	19,54	6	ATH	57	CG1 TPR	8	26,891	38,842	21,190	1,00	11,22	6
5	C VAL	1	13,191	25,013	23,967	1,00	19,86	8	ATH	58	CG2 TPR	8	28,340	39,698	23,424	1,00	10,96	6
6	H VAL	1	10,702	25,241	23,415	1,00	20,28	7	ATH	59	CG2 TPR	8	25,359	40,620	25,153	1,00	11,52	6
7	CA VAL	1	13,627	25,285	23,505	1,00	18,75	7	ATH	60	CG2 TPR	8	25,359	40,620	25,153	1,00	11,52	6
8	CA VAL	2	13,627	25,285	23,505	1,00	18,75	7	ATH	61	CG1 TH	8	27,119	41,065	20,294	1,00	11,87	6
9	CA ASN	2	15,168	24,197	22,212	1,00	16,73	7	ATH	62	C TPR	8	30,786	37,289	24,119	1,00	9,70	6
10	CG ASN	2	15,836	23,657	20,945	1,00	16,09	6	ATH	63	C TPR	8	31,010	38,427	24,563	1,00	9,67	6
11	CG ASN	2	15,219	22,336	20,451	1,00	15,33	6	ATH	64	H PHE	9	31,890	36,710	23,639	1,00	9,16	7
12	CG1 ASN	2	14,707	21,549	19,252	1,00	15,28	8	ATH	65	CA PHE	9	33,191	37,307	23,588	1,00	9,15	6
13	H02 ASN	2	15,283	22,082	19,151	1,00	12,11	7	ATH	66	CB PHE	9	33,191	37,307	23,588	1,00	9,15	6
14	C ASN	2	15,903	22,336	20,398	1,00	16,02	8	ATH	67	CG1 PHE	9	33,191	37,307	23,588	1,00	9,15	6
15	C ASN	2	15,903	22,336	20,398	1,00	16,02	8	ATH	68	CG1 PHE	9	33,191	37,307	23,588	1,00	9,15	6
16	H GLY	3	16,920	25,198	23,833	1,00	14,56	7	ATH	69	CG2 PHE	9	35,239	36,125	26,720	1,00	10,15	6
17	GLY	3	17,541	26,305	24,331	1,00	13,21	6	ATH	70	CG1 PHE	9	32,887	36,171	26,720	1,00	7,79	6
18	C GLY	3	18,940	26,211	23,671	1,00	12,14	6	ATH	71	CG2 PHE	9	35,440	35,161	27,245	1,00	10,23	6
19	O GLY	3	19,498	25,353	23,302	1,00	11,92	8	ATH	72	CZ PHE	9	33,070	35,205	27,669	1,00	7,64	6
20	H THR	4	19,503	27,588	23,499	1,00	10,18	7	ATH	73	CZ PHE	9	34,313	34,698	27,982	1,00	8,17	6
21	H THR	4	19,503	27,588	23,499	1,00	10,18	7	ATH	74	CZ PHE	9	34,313	34,698	27,982	1,00	8,17	6
22	H THR	4	20,731	27,878	23,781	1,00	11,09	6	ATH	75	H GLU	10	33,264	36,856	22,536	1,00	9,38	7
23	CG1 THR	4	19,920	26,828	20,782	1,00	12,31	6	ATH	76	H GLU	10	36,430	36,089	22,006	1,00	9,09	6
24	CG2 THR	4	22,048	27,933	20,693	1,00	10,56	6	ATH	77	CG GLU	10	36,508	36,043	20,513	1,00	7,45	6
25	C THR	4	21,584	28,664	23,633	1,00	10,56	6										

## Appendix 1

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2/27/2010, EAST Version: 2.4.1.1

AT01	107	OH	TWR	A	12	45.854	35.787	20.560	1.00	13.16	8
AT01	108	C	TWR	A	12	39.687	40.574	20.991	1.00	11.38	8
AT01	109	C	TWR	A	12	39.862	41.436	20.132	1.00	11.53	8
AT01	110	N	TWR	A	13	38.630	40.547	21.783	1.00	11.49	7
AT01	111	N	TWR	A	13	37.651	41.556	21.726	1.00	11.47	6
AT01	112	N	TWR	A	13	37.651	41.556	21.726	1.00	11.47	6
AT01	113	CG1	TWR	A	13	35.755	40.794	22.169	1.00	14.85	8
AT01	114	CG2	TWR	A	13	35.755	40.794	22.169	1.00	14.85	8
AT01	115	C	TWR	A	13	38.429	42.880	22.036	1.00	11.41	6
AT01	116	C	TWR	A	13	39.459	42.805	22.840	1.00	11.13	8
AT01	117	N	PRD	A	14	39.254	44.015	21.408	1.00	11.47	6
AT01	118	N	PRD	A	14	39.254	44.015	21.408	1.00	11.47	6
AT01	119	CA	PRD	A	14	38.079	45.243	21.611	1.00	11.44	6
AT01	120	CG	PRD	A	14	38.477	46.296	20.569	1.00	11.60	6
AT01	121	CG	PRD	A	14	37.352	45.564	20.896	1.00	11.77	6
AT01	122	C	PRD	A	14	38.783	45.668	22.993	1.00	11.21	6
AT01	123	C	PRD	A	14	38.783	45.668	22.993	1.00	11.21	6
AT01	124	C	PRD	A	14	38.783	45.668	22.993	1.00	11.21	6
AT01	125	CA	ASH	A	15	39.720	47.304	24.693	1.00	11.02	6
AT01	126	CA	ASH	A	15	41.055	48.247	26.614	1.00	11.27	6
AT01	127	CG	ASH	A	15	40.008	48.358	27.277	1.00	11.89	6
AT01	128	CG1	ASH	A	15	42.158	48.898	26.422	1.00	11.06	6
AT01	129	CG2	ASH	A	15	42.158	48.898	26.422	1.00	11.06	6
AT01	130	C	ASH	A	15	39.932	49.767	24.524	1.00	11.08	6
AT01	131	C	ASH	A	15	39.932	49.767	24.524	1.00	11.08	6
AT01	132	N	ASP	A	16	38.008	48.835	23.905	1.00	10.98	7
AT01	133	CA	ASP	A	16	37.446	50.118	23.529	1.00	11.17	6
AT01	134	CG	ASP	A	16	36.924	50.059	22.068	1.00	11.99	6
AT01	135	CG	ASP	A	16	35.761	49.101	21.873	1.00	12.89	6
AT01	136	CG1	ASP	A	16	35.761	49.101	21.873	1.00	12.89	6
AT01	137	CG2	ASP	A	16	35.761	49.101	21.873	1.00	12.89	6
AT01	138	C	ASP	A	16	36.352	50.518	24.498	1.00	11.03	6
AT01	139	C	ASP	A	16	36.352	50.518	24.498	1.00	11.03	6
AT01	140	N	GLT	A	17	36.013	49.732	25.513	1.00	10.89	7
AT01	141	CA	GLT	A	17	36.972	50.083	26.479	1.00	10.61	6
AT01	142	C	GLT	A	17	37.259	50.522	26.681	1.00	10.65	6
AT01	143	C	GLT	A	17	37.259	50.522	26.681	1.00	10.65	6
AT01	144	N	GLM	A	18	33.287	49.436	24.766	1.00	10.50	7
AT01	145	CA	GLM	A	18	31.995	49.346	24.151	1.00	10.55	6
AT01	146	CG	GLM	A	18	32.084	49.835	22.691	1.00	15.25	6
AT01	147	CG	GLM	A	18	32.718	51.182	22.436	1.00	21.24	6
AT01	148	CG1	GLM	A	18	32.718	51.182	22.436	1.00	21.24	6
AT01	149	CG2	GLM	A	18	32.718	51.182	22.436	1.00	21.24	6
AT01	150	ME2	GLM	A	18	32.004	53.124	23.668	1.00	27.29	7
AT01	151	C	GLM	A	18	31.421	47.936	24.042	1.00	10.94	6
AT01	152	C	GLM	A	18	30.467	47.808	23.281	1.00	9.96	6
AT01	153	N	HIS	A	19	31.986	46.944	24.782	1.00	9.66	7
AT01	154	C	HIS	A	19	32.432	47.512	25.162	1.00	9.40	6
AT01	155	C	HIS	A	19	32.432	47.512	25.162	1.00	9.40	6
AT01	156	CG	HIS	A	19	32.091	43.173	24.563	1.00	6.79	6
AT01	157	CG2	HIS	A	19	31.749	41.987	25.138	1.00	7.93	6
AT01	158	ME1	HIS	A	19	32.116	42.955	23.187	1.00	8.36	7
AT01	159	CE1	HIS	A	19	31.925	41.705	22.909	1.00	8.32	6
AT01	160	ME2	HIS	A	19	216	216	216	1.00	216	216
AT01	161	C	HIS	A	19	216	216	216	1.00	216	216
AT01	162	C	HIS	A	19	216	216	216	1.00	216	216
AT01	163	N	TRP	A	20	216	216	216	1.00	216	216
AT01	164	N	TRP	A	20	216	216	216	1.00	216	216
AT01	165	CG	TRP	A	20	216	216	216	1.00	216	216
AT01	166	CG	TRP	A	20	216	216	216	1.00	216	216
AT01	167	CG2	TRP	A	20	216	216	216	1.00	216	216
AT01	168	CG3	TRP	A	20	216	216	216	1.00	216	216
AT01	169	CG4	TRP	A	20	216	216	216	1.00	216	216
AT01	170	CG5	TRP	A	20	216	216	216	1.00	216	216
AT01	171	CG6	TRP	A	20	216	216	216	1.00	216	216
AT01	172	CG7	TRP	A	20	216	216	216	1.00	216	216
AT01	173	CG8	TRP	A	20	216	216	216	1.00	216	216
AT01	174	CG9	TRP	A	20	216	216	216	1.00	216	216
AT01	175	C	TRP	A	20	216	216	216	1.00	216	216
AT01	176	C	TRP	A	20	216	216	216	1.00	216	216
AT01	177	N	LYS	A	21	216	216	216	1.00	216	216
AT01	178	CA	LYS	A	21	216	216	216	1.00	216	216
AT01	179	CG	LYS	A	21	216	216	216	1.00	216	216
AT01	180	CG	LYS	A	21	216	216	216	1.00	216	216
AT01	181	CG	LYS	A	21	216	216	216	1.00	216	216
AT01	182	CG	LYS	A	21	216	216	216	1.00	216	216
AT01	183	CG	LYS	A	21	216	216	216	1.00	216	216
AT01	184	C	LYS	A	21	216	216	216	1.00	216	216
AT01	185	O	LYS	A	21	216	216	216	1.00	216	216
AT01	186	N	ARG	A	22	216	216	216	1.00	216	216
AT01	187	CA	ARG	A	22	216	216	216	1.00	216	216
AT01	188	CG	ARG	A	22	216	216	216	1.00	216	216
AT01	189	CG	ARG	A	22	216	216	216	1.00	216	216
AT01	190	CG	ARG	A	22	216	216	216	1.00	216	216
AT01	191	CG	ARG	A	22	216	216	216	1.00	216	216
AT01	192	C	ARG	A	22	216	216	216	1.00	216	216
AT01	193	CG	ARG	A	22	216	216	216	1.00	216	216
AT01	194	CG	ARG	A	22	216	216	216	1.00	216	216
AT01	195	C	ARG	A	22	216	216	216	1.00	216	216
AT01	196	CG	ARG	A	22	216	216	216	1.00	216	216
AT01	197	CG	ARG	A	22	216	216	216	1.00	216	216
AT01	198	CG	ARG	A	22	216	216	216	1.00	216	216
AT01	199	CG	ARG	A	22	216	216	216	1.00	216	216
AT01	200	CG	ARG	A	22	216	216	216	1.00	216	216
AT01	201	CG	ARG	A	22	216	216	216	1.00	216	216
AT01	202	CG	ARG	A	22	216	216	216	1.00	216	216
AT01	203	C	ARG	A	22	216	216	216	1.00	216	216
AT01	204	O	ARG	A	22	216	216	216	1.00	216	216
AT01	205	N	GLH	A	24	216	216	216	1.00	216	216
AT01	206	CA	GLH	A	24	216	216	216	1.00	216	216
AT01	207	CG	GLH	A	24	216	216	216	1.00	216	216
AT01	208	CG	GLH	A	24	216	216	216	1.00	216	216
AT01	209	CG	GLH	A	24	216	216	216	1.00	216	216
AT01	210	CG	GLH	A	24	216	216	216	1.00	216	216
AT01	211	CG	GLH	A	24	216	216	216	1.00	216	216
AT01	212	C	GLH	A	24	216	216	216	1.00	216	216
AT01	213	C	GLH	A	24	216	216	216	1.00	216	216
AT01	214	C	GLH	A	24	216	216	216	1.00	216	216
AT01	215	C	GLH	A	24	216	216	216	1.00	216	216
AT01	216	C	GLH	A	24	216	216	216	1.00	216	216
AT01	217	C	GLH	A	24	216	216	216	1.00	216	216
AT01	218	C	GLH	A	24	216	216	216	1.00	216	216
AT01	219	C	GLH	A	24	216	216	216	1.00	216	216
AT01	220	C	GLH	A	24	216	216	216	1.00	216	216
AT01	221	C	GLH	A	24	216	216	216	1.00	216	216
AT01	222	C	GLH	A	24	216	216	216	1.00	216	216
AT01	223	C	GLH	A	24	216	216	216	1.00	216	216
AT01	224	C	GLH	A	24	216	216	216	1.00	216	216
AT01	225	C	GLH	A	24	216	216	216	1.00	216	216
AT01	226	C	GLH	A	24	216	216	216	1.00	216	216
AT01	227	C	GLH	A	24	216	216	216	1.00	216	216
AT01	228	C	GLH	A	24	216	216	216	1.00	216	216
AT01	229	C	GLH	A	24	216	216	216	1.00	216	216
AT01	230	C	GLH	A	24	216	216	216	1.00	216	216
AT01	231	C	GLH	A	24	216	216	216	1.00	216	216

213	O	GLN	A	24	21.030	45.626	22.296	1.00	14.63	8	ATOM	266	C	SER	A	31	15.995	36.112	18.852	1.00	14.34	6
214	N	ASN	A	25	23.034	46.369	21.594	1.00	14.90	7	ATOM	267	H	SER	A	32	16.021	36.882	17.765	1.00	16.30	7
215	CB	ASN	A	25	22.642	46.325	20.213	1.00	15.31	6	ATOM	268	CA	ASP	A	32	15.427	36.341	16.518	1.00	16.55	6
216	CB	ASN	A	25	23.711	46.719	19.680	1.00	22.28	8	ATOM	269	CA	ASP	A	32	15.485	37.339	15.370	1.00	22.70	6
217	MOI	ASN	A	25	22.686	49.238	20.127	1.00	24.44	8	ATOM	271	CG	ASP	A	32	14.756	38.665	15.583	1.00	27.13	8
218	CB	ASN	A	25	22.371	45.141	19.568	1.00	23.11	6	ATOM	272	CG	ASP	A	32	13.869	38.871	16.443	1.00	27.33	8
219	CB	ASN	A	25	22.562	45.198	18.637	1.00	15.19	6	ATOM	273	CG	ASP	A	32	15.122	39.661	14.868	1.00	27.28	8
220	CB	ASN	A	25	22.647	42.725	19.101	1.00	14.46	6	ATOM	274	CG	ASP	A	32	15.416	36.249	15.583	1.00	16.54	8
221	O	ASN	A	25	24.002	42.002	19.440	1.00	14.63	6	ATOM	276	H	ILE	A	33	17.519	34.662	16.111	1.00	15.83	7
222	N	ASP	A	26	23.651	41.073	17.292	1.00	14.77	8	ATOM	277	CA	ILE	A	33	18.093	33.612	15.639	1.00	15.16	6
223	CB	ASP	A	26	25.294	40.238	18.363	1.00	14.45	8	ATOM	278	CB	ILE	A	33	19.570	33.906	15.292	1.00	13.80	6
224	CB	ASP	A	26	21.119	40.869	19.454	1.00	15.76	8	ATOM	280	CG	ILE	A	33	18.581	34.904	14.219	1.00	11.62	6
225	CB	ASP	A	26	20.813	42.356	20.086	1.00	14.32	7	ATOM	281	CG	ILE	A	33	21.832	34.372	16.151	1.00	14.13	6
226	CB	ASP	A	26	19.761	41.641	21.661	1.00	14.78	6	ATOM	283	O	ILE	A	33	17.939	32.608	16.568	1.00	15.00	6
227	CB	ALA	A	27	19.276	42.463	22.849	1.00	12.97	6	ATOM	284	H	GLY	A	34	18.342	31.264	16.207	1.00	15.20	8
228	CB	ALA	A	27	18.627	41.207	20.754	1.00	15.34	6	ATOM	285	CA	GLY	A	34	17.303	32.527	17.740	1.00	14.35	7
229	CB	ALA	A	27	18.231	43.083	20.840	1.00	15.76	7	ATOM	286	CA	GLY	A	34	17.113	31.390	18.606	1.00	13.52	6
230	CB	ALA	A	27	17.410	40.667	18.846	1.00	15.25	6	ATOM	287	CA	GLY	A	34	18.034	31.510	20.453	1.00	12.97	6
231	CB	GLU	A	28	17.010	41.598	18.984	1.00	16.05	6	ATOM	288	H	ILE	A	35	18.796	32.268	20.120	1.00	12.23	7
232	CB	GLU	A	28	16.526	42.815	18.170	1.00	23.00	6	ATOM	289	CA	ILE	A	35	19.679	32.268	21.301	1.00	11.16	6
233	CB	GLU	A	28	15.097	42.736	17.596	1.00	31.01	6	ATOM	290	CB	ILE	A	35	20.812	33.277	21.168	1.00	9.45	6
234	CB	GLU	A	28	14.001	42.258	18.547	1.00	36.48	6	ATOM	291	CG	ILE	A	35	21.595	33.376	22.527	1.00	8.10	6
235	CB	GLU	A	28	13.644	41.913	18.597	1.00	40.16	8	ATOM	292	CG	ILE	A	35	21.782	33.025	20.002	1.00	9.07	6
236	CB	GLU	A	28	17.410	40.667	18.846	1.00	15.25	6	ATOM	293	CG	ILE	A	35	18.796	32.268	22.516	1.00	10.71	6
237	CB	GLU	A	28	16.773	39.455	17.835	1.00	15.57	8	ATOM	295	O	ILE	A	35	18.050	33.521	22.586	1.00	10.45	8
238	CB	GLU	A	28	19.577	40.712	17.415	1.00	15.36	7	ATOM	296	H	ILE	A	35	18.816	31.638	21.519	1.00	10.23	7
239	CB	GLU	A	28	19.158	39.769	16.461	1.00	15.11	6	ATOM	297	CA	THR	A	36	18.010	31.768	24.713	1.00	9.85	6
240	CB	GLU	A	28	20.492	40.422	16.008	1.00	16.22	6	ATOM	298	CB	THR	A	36	17.144	30.482	24.943	1.00	7.65	6
241	CB	GLU	A	28	20.895	38.301	16.294	1.00	18.16	6	ATOM	299	CG	THR	A	36	18.091	29.495	25.089	1.00	7.88	8
242	CB	GLU	A	28	20.895	38.301	16.294	1.00	18.16	6	ATOM	300	CG	THR	A	36	18.164	32.126	25.955	1.00	9.70	6
243	O	GLU	A	29	22.639	39.155	15.496	1.00	18.52	7	ATOM	301	C	THR	A	36	18.271	32.449	26.995	1.00	9.82	8
244	N	HIS	A	29	23.055	38.163	16.493	1.00	18.61	6	ATOM	303	O	THR	A	36	20.160	32.045	25.937	1.00	9.41	7
245	CA	HIS	A	29	22.066	37.741	13.984	1.00	18.61	7	ATOM	304	CA	ALA	A	37	20.570	32.392	27.086	1.00	9.45	6
246	CB	HIS	A	29	19.282	38.370	17.059	1.00	14.84	6	ATOM	305	CA	ALA	A	37	21.609	31.279	28.113	1.00	5.60	6
247	CB	HIS	A	29	19.952	37.392	16.153	1.00	14.66	7	ATOM	306	C	ALA	A	37	22.389	32.897	26.536	1.00	9.43	6
248	CB	HIS	A	29	20.154	37.107	19.020	1.00	14.56	6	ATOM	307	H	VAL	A	38	22.971	33.921	27.171	1.00	9.33	7
249	CB	LEU	A	30	20.913	37.409	20.319	1.00	13.60	6	ATOM	308	H	VAL	A	38	24.164	34.496	26.851	1.00	9.68	6
250	CB	LEU	A	30	22.350	37.884	20.194	1.00	15.00	6	ATOM	309	CA	VAL	A	38	24.047	35.995	26.455	1.00	12.81	6
251	CB	LEU	A	30	23.018	37.967	21.586	1.00	15.90	6	ATOM	311	CG	VAL	A	38	23.387	36.191	25.123	1.00	12.91	6
252	CB	LEU	A	30	22.273	37.049	19.799	1.00	14.74	6	ATOM	312	CG	VAL	A	38	25.700	34.566	25.102	1.00	9.49	6
253	O	LEU	A	30	19.683	35.228	19.248	1.00	14.21	8	ATOM	314	H	TRP	A	39	26.371	33.015	27.799	1.00	9.06	7
254	CB	LEU	A	30	17.877	37.240	19.879	1.00	15.37	7	ATOM	315	H	TRP	A	39	26.474	33.825	28.774	1.00	8.66	6
255	CB	LEU	A	30	16.596	36.559	20.204	1.00	16.15	6	ATOM	316	CA	TRP	A	39	28.188	32.892	28.787	1.00	7.43	6
256	CB	SER	A	31	15.603	37.378	21.005	1.00	17.82	6	ATOM	317	CB	TRP	A	39	29.412	32.554	29.282	1.00	6.23	6
257	OG	SER	A	31	15.358	38.328	20.190	1.00	22.98	8	ATOM	318	CG	TRP	A	39						

Alum	319	CG2	TRP	A	39	30.401	31.462	38.807	1.00	6.00	6
Alum	320	CE3	TRP	A	39	31.875	32.565	27.008	1.00	5.50	6
Alum	321	CE3	TRP	A	39	30.708	30.585	27.008	1.00	5.50	6
Alum	322	CG1	TRP	A	39	30.201	33.372	30.190	1.00	5.74	6
Alum	323	NE1	TRP	A	39	31.568	33.153	30.268	1.00	5.57	7
Alum	324	CG2	TRP	A	39	31.099	31.441	29.211	1.00	5.00	6
Alum	325	CG2	TRP	A	39	31.155	29.964	27.701	1.00	5.00	6
Alum	326	CG2	TRP	A	39	31.155	29.964	27.701	1.00	5.00	6
Alum	327	O	TRP	A	39	28.317	35.078	28.452	1.00	8.50	6
Alum	328	O	TRP	A	39	28.856	35.078	27.384	1.00	8.32	6
Alum	329	N	ILE	A	40	28.431	35.945	29.659	1.00	8.31	7
Alum	330	CA	ILE	A	40	29.163	37.247	29.647	1.00	8.57	6
Alum	331	CG2	ILE	A	40	28.103	36.113	30.139	1.00	9.85	6
Alum	332	CG2	ILE	A	40	28.089	36.113	30.139	1.00	9.85	6
Alum	333	CG1	ILE	A	40	27.803	39.287	29.286	1.00	9.52	6
Alum	334	CG1	ILE	A	40	26.594	36.637	28.616	1.00	11.76	6
Alum	335	C	ILE	A	40	30.524	37.121	30.063	1.00	8.39	6
Alum	336	O	ILE	A	40	30.680	36.373	31.033	1.00	8.04	8
Alum	337	O	ILE	A	40	31.271	37.000	29.564	1.00	8.30	7
Alum	338	O	ILE	A	40	31.271	37.000	29.564	1.00	8.30	7
Alum	339	CA	PRO	A	41	32.807	37.771	30.151	1.00	8.16	6
Alum	340	CA	PRO	A	41	33.802	36.683	29.246	1.00	8.13	6
Alum	341	CG	PRO	A	41	32.756	39.565	28.595	1.00	8.01	6
Alum	342	C	PRO	A	41	32.864	38.312	28.595	1.00	7.87	6
Alum	343	H	PRO	A	42	31.091	38.952	32.039	1.00	7.72	8
Alum	344	H	PRO	A	42	31.091	38.952	32.039	1.00	7.72	8
Alum	345	H	PRO	A	42	35.113	37.207	31.880	1.00	7.34	6
Alum	346	CA	PRO	A	42	34.084	38.562	33.711	1.00	7.41	6
Alum	347	CB	PRO	A	42	35.490	38.085	34.191	1.00	7.45	6
Alum	348	CG	PRO	A	42	35.772	36.947	33.217	1.00	7.45	6
Alum	349	C	PRO	A	42	31.851	40.054	33.685	1.00	7.06	6
Alum	350	C	PRO	A	42	32.867	44.042	35.582	1.00	6.42	8
Alum	351	N	ALA	A	43	32.875	40.538	32.451	1.00	6.75	9
Alum	352	CA	ALA	A	43	32.477	41.937	34.481	1.00	6.39	6
Alum	353	CB	ALA	A	43	30.968	41.991	34.756	1.00	5.00	6
Alum	354	C	ALA	A	43	33.131	42.865	35.529	1.00	6.36	6
Alum	355	C	ALA	A	43	32.867	44.042	35.582	1.00	6.42	8
Alum	356	CA	TRP	A	44	34.637	42.182	37.246	1.00	6.22	7
Alum	357	CA	TRP	A	44	34.637	42.182	37.246	1.00	6.22	7
Alum	358	CG	TRP	A	44	34.381	40.781	38.819	1.00	6.51	6
Alum	359	CG	TRP	A	44	34.381	40.781	38.819	1.00	6.51	6
Alum	360	CG1	TRP	A	44	35.538	40.086	38.145	1.00	6.67	6
Alum	361	CG1	TRP	A	44	33.472	38.727	37.848	1.00	6.66	6
Alum	362	CG1	TRP	A	44	33.472	38.727	37.848	1.00	6.66	6
Alum	363	CG2	TRP	A	44	33.108	38.072	38.501	1.00	6.52	6
Alum	364	CG2	TRP	A	44	34.276	38.073	37.917	1.00	6.98	6
Alum	365	OH	TRP	A	44	34.209	38.729	37.568	1.00	7.43	8
Alum	366	C	TRP	A	44	36.060	43.413	37.075	1.00	5.99	6
Alum	367	N	TRP	A	44	35.582	42.945	36.097	1.00	5.98	7
Alum	368	N	TRP	A	44	35.582	42.945	36.097	1.00	5.98	7
Alum	369	CA	LYS	A	45	37.865	45.303	37.518	1.00	5.73	6
Alum	370	CG	LYS	A	45	36.033	46.160	38.580	1.00	5.00	6
Alum	371	CG	LYS	A	45	39.192	47.127	38.251	1.00	5.00	6
Alum	372	CE	LYS	A	45	39.093	48.021	37.024	1.00	5.00	6
Alum	373	CG	LYS	A	45	37.030	48.865	36.976	1.00	5.00	6
Alum	374	CG	LYS	A	45	37.030	48.865	36.976	1.00	5.00	6
Alum	375	C	LYS	A	45	39.209	44.011	37.459	1.00	5.00	7
Alum	376	C	LYS	A	45	39.209	44.011	37.459	1.00	5.00	7
Alum	377	GLY	A	46	39.887	43.306	38.436	1.00	5.70	8	
Alum	378	CA	GLY	A	46	39.887	43.306	38.436	1.00	5.70	8
Alum	379	C	GLY	A	46	41.017	43.169	36.408	1.00	6.09	7
Alum	380	C	GLY	A	46	41.017	43.169	36.408	1.00	6.09	7
Alum	381	C	GLY	A	46	42.246	43.917	36.957	1.00	7.41	6
Alum	382	CA	LEU	A	47	42.246	43.917	36.957	1.00	7.41	6
Alum	383	CB	LEU	A	47	42.246	43.917	36.957	1.00	7.41	6
Alum	384	CB	LEU	A	47	44.481	43.889	37.305	1.00	6.74	7
Alum	385	CB	LEU	A	47	44.481	43.889	37.305	1.00	6.74	7
Alum	386	CB	LEU	A	47	44.481	43.889	37.305	1.00	6.74	7
Alum	387	CB	LEU	A	47	44.481	43.889	37.305	1.00	6.74	7
Alum	388	CB	LEU	A	47	44.481	43.889	37.305	1.00	6.74	7
Alum	389	CB	LEU	A	47	44.481	43.889	37.305	1.00	6.74	7
Alum	390	CB	LEU	A	47	44.481	43.889	37.305	1.00	6.74	7
Alum	391	CB	LEU	A	47	44.481	43.889	37.305	1.00	6.74	7
Alum	392	CB	LEU	A	47	44.481	43.889	37.305	1.00	6.74	7
Alum	393	CB	LEU	A	47	44.481	43.889	37.305	1.00	6.74	7
Alum	394	CB	LEU	A	47	44.481	43.889	37.305	1.00	6.74	7
Alum	395	CB	LEU	A	47	44.481	43.889	37.305	1.00	6.74	7
Alum	396	CB	LEU	A	47	44.481	43.889	37.305	1.00	6.74	7
Alum	397	CB	LEU	A	47	44.481	43.889	37.305	1.00	6.74	7
Alum	398	CB	LEU	A	47	44.481	43.889	37.305	1.00	6.74	7
Alum	399	CB	LEU	A	47	44.481	43.889	37.305	1.00	6.74	7
Alum	400	CE1	GLN	A	49	41.078	51.178	30.061	1.00	7.48	6
Alum	401	CE2	GLN	A	49	41.078	51.178	30.061	1.00	7.48	6
Alum	402	C	GLN	A	49	40.489	52.271	31.003	1.00	7.62	8
Alum	403	C	GLN	A	49	40.489	52.271	31.003	1.00	7.62	8
Alum	404	C	GLN	A	49	40.774	46.745	30.647	1.00	9.52	8
Alum	405	C	GLN	A	49	40.774	46.745	30.647	1.00	9.52	8
Alum	406	C	GLN	A	49	40.774	46.745	30.647	1.00	9.52	8
Alum	407	C	GLN	A	49	40.774	46.745	30.647	1.00	9.52	8
Alum	408	C	GLN	A	49	40.774	46.745	30.647	1.00	9.52	8
Alum	409	C	GLN	A	49	40.774	46.745	30.647	1.00	9.52	8
Alum	410	C	GLN	A	49	40.774	46.745	30.647	1.00	9.52	8
Alum	411	C	GLN	A	49	40.774	46.745	30.647	1.00	9.52	8
Alum	412	C	GLN	A	49	40.774	46.745	30.647	1.00	9.52	8
Alum	413	C	GLN	A	49	40.774	46.745	30.647	1.00	9.52	8
Alum	414	C	GLN	A	49	40.774	46.745	30.647	1.00	9.52	8
Alum	415	C	GLN	A	49	40.774	46.745	30.647	1.00	9.52	8
Alum	416	C	GLN	A	49	40.774	46.745	30.647	1.00	9.52	8
Alum	417	C	GLN	A	49	40.774	46.745	30.647	1.00	9.52	8
Alum	418	C	GLN	A	49	40.774	46.745	30.647	1.00	9.52	8
Alum	419	C	GLN	A	49	40.774	46.745	30.647	1.00	9.52	8
Alum	420	C	GLN	A	49	40.774	46.745	30.647	1.00	9.52	8
Alum	421	C	GLN	A	49	40.774	46.745	30.647	1.00	9.52	8
Alum	422	C	GLN	A	49	40.774	46.745	30.647	1.00	9.52	8
Alum	423	C	GLN	A	49	40.774	46.745	30.647	1.00	9.52	8
Alum	424	C	GLN	A	49	40.774	46.745	30.647	1.00	9.52	8

425	ATON	425	O	ASN	A	52	38,007	39,399	30,782	1,00	7,11	8
426	ATON	426	N	GLY	A	53	39,452	39,949	32,309	1,00	6,67	7
427	ATON	427	CA	GLY	A	53	38,832	39,609	33,457	1,00	6,62	6
428	ATON	428	C	GLY	A	53	39,262	38,324	33,124	1,00	6,62	6
429	ATON	429	H	GLY	A	52	39,262	38,324	33,124	1,00	6,62	6
430	ATON	430	H	GLY	A	52	40,222	37,565	33,544	1,00	6,58	7
431	ATON	431	CA	GLY	A	54	40,722	36,331	33,179	1,00	5,98	6
432	ATON	432	CB	GLY	A	54	41,027	35,227	33,116	1,00	6,06	6
433	ATON	433	CB	GLY	A	54	39,720	34,834	32,427	1,00	5,99	6
434	ATON	434	CD	GLY	A	54	39,481	35,232	33,108	1,00	6,44	6
435	ATON	435	CD	GLY	A	54	38,700	34,199	32,802	1,00	5,97	6
436	ATON	436	CD	GLY	A	54	38,700	34,199	32,802	1,00	5,97	6
437	ATON	437	CD	GLY	A	54	37,474	33,057	32,517	1,00	6,05	6
438	ATON	438	CD	GLY	A	54	37,282	34,209	33,158	1,00	6,50	6
439	ATON	439	CD	GLY	A	54	36,083	33,028	30,582	1,00	6,09	6
440	ATON	440	C	GLY	A	54	41,079	36,549	35,185	1,00	5,76	6
441	ATON	441	C	GLY	A	54	41,079	36,549	35,185	1,00	5,76	6
442	ATON	442	H	GLY	A	55	42,337	37,799	35,429	1,00	5,53	7
443	ATON	443	CA	GLY	A	55	43,226	38,205	36,438	1,00	5,64	6
444	ATON	444	C	GLY	A	55	42,464	39,315	37,256	1,00	5,59	6
445	ATON	445	O	GLY	A	55	42,818	40,499	37,213	1,00	5,60	8
446	ATON	446	H	PRO	A	56	41,410	39,876	37,948	1,00	5,20	7
447	ATON	447	H	PRO	A	56	40,562	39,257	38,732	1,00	5,12	6
448	ATON	448	CA	PRO	A	56	40,562	39,257	38,732	1,00	5,12	6
449	ATON	449	CB	PRO	A	56	39,282	38,948	39,083	1,00	5,13	6
450	ATON	450	CB	PRO	A	56	39,914	37,555	39,212	1,00	5,03	6
451	ATON	451	C	PRO	A	56	41,189	40,355	39,998	1,00	5,03	6
452	ATON	452	O	PRO	A	56	41,728	39,671	40,862	1,00	5,00	8
453	ATON	453	A	TIR	A	57	41,191	40,640	40,207	1,00	5,00	7
454	ATON	454	A	TIR	A	57	41,191	40,640	40,207	1,00	5,00	7
455	ATON	455	CB	TIR	A	57	42,042	43,842	40,709	1,00	5,45	6
456	ATON	456	CG	TIR	A	57	42,261	43,842	41,800	1,00	6,29	6
457	ATON	457	CG	TIR	A	57	43,330	44,634	42,730	1,00	6,86	6
458	ATON	458	CG	TIR	A	57	43,521	45,499	43,810	1,00	7,20	6
459	ATON	459	CG	TIR	A	57	41,521	42,973	42,014	1,00	6,52	6
460	ATON	460	CG	TIR	A	57	41,521	42,973	42,014	1,00	6,52	6
461	ATON	461	CZ	TIR	A	57	42,669	46,566	43,983	1,00	7,37	6
462	ATON	462	OH	TIR	A	57	42,835	47,431	45,036	1,00	7,85	6
463	ATON	463	C	TIR	A	57	40,372	42,683	42,201	1,00	5,00	6
464	ATON	464	O	TIR	A	57	40,546	42,347	43,362	1,00	5,00	8
465	ATON	465	A	ASP	A	58	39,710	42,212	43,726	1,00	5,00	7
466	ATON	466	A	ASP	A	58	39,710	42,212	43,726	1,00	5,00	7
467	ATON	467	CB	ASP	A	58	38,136	44,990	43,088	1,00	5,00	6
468	ATON	468	CB	ASP	A	58	37,210	45,478	44,152	1,00	5,00	6
469	ATON	469	CD	ASP	A	58	36,550	44,681	42,991	1,00	5,00	8
470	ATON	470	CD	ASP	A	58	36,995	46,702	44,348	1,00	5,00	8
471	ATON	471	C	ASP	A	58	36,913	42,974	42,259	1,00	5,00	6
472	ATON	472	N	LEU	A	59	36,258	41,917	42,874	1,00	5,00	7
473	ATON	473	N	LEU	A	59	36,258	41,917	42,874	1,00	5,00	7
474	ATON	474	CB	LEU	A	59	34,696	41,399	42,426	1,00	5,00	6
475	ATON	475	CB	LEU	A	59	34,696	41,399	42,426	1,00	5,00	6
476	ATON	476	CD	LEU	A	59	35,472	38,942	42,805	1,00	8,19	6
477	ATON	477	CD	LEU	A	59	35,472	38,942	42,805	1,00	8,19	6
478	ATON	478	CD	LEU	A	59	35,960	38,571	41,423	1,00	6,96	6
479	ATON	479	C	LEU	A	59	33,758	42,112	42,650	1,00	5,05	8
480	ATON	480	O	LEU	A	59	32,644	42,112	42,650	1,00	5,05	8
481	ATON	481	H	TIR	A	60	33,921	43,352	43,480	1,00	5,25	7
482	ATON	482	H	TIR	A	60	32,814	44,611	43,480	1,00	5,22	6
483	ATON	483	CB	TIR	A	60	32,814	44,611	43,480	1,00	5,22	6
484	ATON	484	CB	TIR	A	60	32,214	43,597	46,224	1,00	5,38	6
485	ATON	485	CG	TIR	A	60	33,101	42,761	46,929	1,00	5,65	6
486	ATON	486	CG	TIR	A	60	32,644	41,833	47,866	1,00	5,22	6
487	ATON	487	CG	TIR	A	60	30,855	43,441	46,441	1,00	5,22	6
488	ATON	488	CG	TIR	A	60	30,855	43,441	46,441	1,00	5,22	6
489	ATON	489	CG	TIR	A	60	30,855	43,441	46,441	1,00	5,22	6
490	ATON	490	CG	TIR	A	60	30,867	40,766	46,957	1,00	6,71	8
491	ATON	491	C	TIR	A	60	32,888	45,540	42,937	1,00	5,77	6
492	ATON	492	O	TIR	A	60	32,117	46,467	43,158	1,00	6,16	8
493	ATON	493	N	ASP	A	61	33,824	45,890	42,052	1,00	5,53	7
494	ATON	494	N	ASP	A	61	33,824	45,890	42,052	1,00	5,53	7
495	ATON	495	CB	ASP	A	61	35,399	47,325	41,106	1,00	6,02	6
496	ATON	496	CB	ASP	A	61	35,635	48,569	40,256	1,00	5,28	6
497	ATON	497	CD	ASP	A	61	34,717	49,013	39,668	1,00	6,54	8
498	ATON	498	CD	ASP	A	61	36,778	49,132	40,283	1,00	5,00	8
499	ATON	499	C	ASP	A	61	33,455	46,390	39,790	1,00	6,20	6
500	ATON	500	O	LEU	A	62	35,113	45,864	39,005	1,00	6,25	8
501	ATON	501	O	LEU	A	62	35,113	45,864	39,005	1,00	6,25	8
502	ATON	502	CA	LEU	A	62	31,732	46,208	38,072	1,00	6,80	6
503	ATON	503	CB	LEU	A	62	30,242	45,815	38,193	1,00	7,43	6
504	ATON	504	CB	LEU	A	62	29,864	44,704	39,231	1,00	9,12	6
505	ATON	505	CG	LEU	A	62	28,372	44,443	39,402	1,00	6,08	6
506	ATON	506	CG	LEU	A	62	30,514	43,357	38,809	1,00	9,37	6
507	ATON	507	C	LEU	A	62	31,934	47,317	37,053	1,00	7,56	6
508	ATON	508	C	LEU	A	62	32,008	48,246	39,004	1,00	7,06	7
509	ATON	509	N	GLY	A	63	32,008	48,246	39,004	1,00	7,06	7
510	ATON	510	CA	GLY	A	63	33,125	49,350	36,307	1,00	7,99	6
511	ATON	511	C	GLY	A	63	32,529	50,656	36,862	1,00	8,19	6
512	ATON	512	O	GLY	A	63	31,954	51,380	36,064	1,00	8,78	7
513	ATON	513	N	GLY	A	64	32,685	50,974	38,143	1,00	7,99	6
514	ATON	514	CB	GLY	A	64	32,154	52,244	38,059	1,00	9,55	6
515	ATON	515	CB	GLY	A	64	32,154	52,244	38,059	1,00	9,55	6
516	ATON	516	CG	GLY	A	64	30,916	51,052	40,317	1,00	10,26	6
517	ATON	517	CD	GLY	A	64	29,629	50,986	41,287	1,00	13,83	8
518	ATON	518	CG	GLY	A	64	29,203	49,959	41,856	1,00	16,12	8
519	ATON	519	CG	GLY	A	64	28,864	51,950	41,397	1,00	15,85	8
520	ATON	520	C	GLY	A	64	33,064	52,958	39,664	1,00	9,91	8
521	ATON	521	C	GLY	A	64	33,064	52,958	39,664	1,00	9,91	8
522	ATON	522	N	PHE	A	65	34,212	52,363	39,542	1,00	10,88	7
523	ATON	523	CA	PHE	A	65	35,172	52,891	40,486	1,00	10,39	6
524	ATON	524	CB	PHE	A	65	35,412	51,981	42,114	1,00	9,02	6
525	ATON	525	CB	PHE	A	65	34,151	51,662	42,878	1,00	8,75	6
526	ATON	526	CG	PHE	A	65	33,541	50,420	42,829	1,00	7,83	6
527	ATON	527	CG	PHE	A	65	33,541	50,420	42,829	1,00	7,83	6
528	ATON	528	CG	PHE	A	65	33,541	50,420	42,829	1,00	7,83	6
529	ATON	529	CZ	PHE	A	65	32,322	52,406	44,788	1,00	6,31	6
530	ATON	530	CZ	PHE	A	65	31,739	51,138	44,248	1,00	5,83	6

ATOM	531	C	PHE A	65	36.480	53.123	40.126	1.00	10.75	6
ATOM	532	O	PHE A	65	36.935	52.381	39.255	1.00	10.67	8
ATOM	533	CA	GLU A	66	37.091	54.715	40.964	1.00	11.02	7
ATOM	534	CA	GLU A	66	38.370	54.390	39.964	1.00	11.57	6
ATOM	535	CB	GLU A	66	38.415	54.361	39.964	1.00	11.57	6
ATOM	536	CB	GLU A	66	39.855	52.415	39.255	1.00	20.55	6
ATOM	537	CD	GLU A	66	40.150	54.793	39.383	1.00	24.82	6
ATOM	538	OE1	GLU A	66	39.958	57.012	37.688	1.00	28.84	7
ATOM	539	NE2	GLU A	66	40.716	55.780	37.719	1.00	26.86	8
ATOM	540	C	GLU A	66	39.489	53.768	40.576	1.00	11.54	6
ATOM	541	CA	GLU A	66	39.870	53.689	39.964	1.00	11.57	7
ATOM	542	CA	GLU A	69	39.870	53.689	39.964	1.00	11.57	7
ATOM	543	CA	GLU A	67	40.915	51.766	40.121	1.00	11.24	6
ATOM	544	CA	GLU A	67	40.390	50.591	41.201	1.00	9.56	6
ATOM	545	CG	GLU A	67	39.353	50.740	42.242	1.00	7.94	6
ATOM	546	CG	GLU A	67	38.970	49.495	43.240	1.00	9.97	6
ATOM	547	CG	GLU A	67	38.970	49.495	43.240	1.00	9.97	6
ATOM	548	NE2	GLU A	67	38.222	48.659	42.932	1.00	5.05	7
ATOM	549	C	GLU A	67	41.728	51.546	39.242	1.00	11.63	6
ATOM	550	O	GLU A	67	41.158	50.567	38.216	1.00	11.46	8
ATOM	551	N	LYS A	68	43.063	51.169	39.341	1.00	12.11	7
ATOM	552	CA	LYS A	68	43.938	50.664	38.285	1.00	12.61	6
ATOM	553	CB	LYS A	68	43.465	48.179	38.780	1.00	12.46	6
ATOM	554	CB	LYS A	68	44.715	48.024	39.626	1.00	15.01	6
ATOM	555	CD	LYS A	68	44.683	47.235	40.918	1.00	14.26	6
ATOM	556	CE	LYS A	68	44.683	47.235	40.918	1.00	14.26	6
ATOM	557	CE	LYS A	68	46.062	47.066	41.499	1.00	12.89	7
ATOM	558	N	LYS A	68	43.908	51.710	37.178	1.00	13.39	6
ATOM	559	CA	LYS A	68	43.725	51.725	37.178	1.00	13.39	6
ATOM	560	CA	LYS A	69	43.725	51.725	37.178	1.00	13.39	6
ATOM	561	CA	LYS A	69	43.725	51.725	37.178	1.00	13.39	6
ATOM	562	C	LYS A	69	42.535	54.177	35.674	1.00	12.59	6
ATOM	563	D	LYS A	69	42.481	54.975	34.735	1.00	12.74	8
ATOM	564	N	LYS A	70	41.497	53.394	35.983	1.00	12.05	7
ATOM	565	CA	LYS A	70	41.497	53.394	35.983	1.00	12.05	7
ATOM	566	CA	LYS A	70	40.554	52.315	35.123	1.00	10.99	6
ATOM	567	CB	LYS A	70	40.554	52.315	35.123	1.00	10.99	6
ATOM	568	CB	LYS A	70	39.502	52.310	33.773	1.00	10.12	8
ATOM	569	CD	LYS A	70	39.502	52.310	33.773	1.00	10.12	8
ATOM	570	CE	LYS A	70	39.087	53.169	35.950	1.00	10.63	6
ATOM	571	CE	LYS A	70	37.015	52.264	36.977	1.00	10.42	8
ATOM	572	CE	LYS A	70	37.015	52.264	36.977	1.00	10.42	8
ATOM	573	CA	VAL A	71	36.600	53.749	36.107	1.00	9.76	6
ATOM	574	CB	VAL A	71	35.802	54.168	35.985	1.00	10.20	6
ATOM	575	CD	VAL A	71	34.374	54.448	36.303	1.00	8.33	6
ATOM	576	CE	VAL A	71	36.393	55.660	36.919	1.00	9.35	6
ATOM	577	CE	VAL A	71	36.923	52.313	35.404	1.00	9.37	6
ATOM	578	N	ARG A	72	36.087	52.567	35.080	1.00	8.79	7
ATOM	579	CA	ARG A	72	35.449	51.252	33.344	1.00	8.64	6
ATOM	580	CB	ARG A	72	35.205	51.645	33.846	1.00	7.09	6
ATOM	581	CG	ARG A	72	36.453	51.798	30.962	1.00	6.38	6
ATOM	582	CG	ARG A	72	36.453	51.798	30.962	1.00	6.38	6
ATOM	583	NE	ARG A	72	31.131	52.071	28.536	1.00	6.51	7
ATOM	584	CZ	ARG A	72	38.926	51.266	28.054	1.00	5.00	6
ATOM	585	HN1	ARG A	72	38.926	51.266	28.054	1.00	5.00	6
ATOM	586	HN2	ARG A	72	38.043	50.022	28.506	1.00	5.00	7
ATOM	587	C	ARG A	72	36.316	49.984	33.347	1.00	8.29	6
ATOM	588	CA	ARG A	72	37.321	49.984	33.347	1.00	8.29	6
ATOM	589	CA	ARG A	72	37.321	49.984	33.347	1.00	8.29	6
ATOM	590	CA	THR A	73	36.539	47.432	32.967	1.00	8.12	7
ATOM	591	CB	THR A	73	35.820	46.301	33.210	1.00	5.35	8
ATOM	592	CG	THR A	73	34.727	46.140	33.217	1.00	5.35	8
ATOM	593	CG	THR A	73	35.361	46.223	34.730	1.00	5.00	6
ATOM	594	C	THR A	73	36.932	47.628	31.481	1.00	8.12	6
ATOM	595	CA	LYS A	74	37.131	46.571	30.519	1.00	8.08	7
ATOM	596	CA	LYS A	74	37.131	46.571	30.519	1.00	8.08	7
ATOM	597	CA	LYS A	74	37.782	46.496	29.508	1.00	8.07	6
ATOM	598	CG	LYS A	74	38.443	45.122	29.215	1.00	7.37	6
ATOM	599	CG	LYS A	74	38.780	44.864	27.777	1.00	7.51	6
ATOM	600	CG	LYS A	74	39.443	43.445	27.359	1.00	6.71	6
ATOM	601	CG	LYS A	74	39.443	43.445	27.359	1.00	6.71	6
ATOM	602	H2	LYS A	74	40.043	42.121	25.465	1.00	7.92	7
ATOM	603	C	LYS A	74	36.469	46.596	28.696	1.00	7.96	6
ATOM	604	O	LYS A	74	36.376	47.163	27.598	1.00	7.92	8
ATOM	605	N	THR A	75	35.375	46.004	29.221	1.00	7.80	7
ATOM	606	CA	THR A	75	34.113	45.937	28.503	1.00	7.58	6
ATOM	607	CA	THR A	75	34.113	45.937	28.503	1.00	7.58	6
ATOM	608	CG	THR A	75	34.311	45.650	28.024	1.00	7.14	6
ATOM	609	CG	THR A	75	34.311	45.650	28.024	1.00	7.14	6
ATOM	610	CD	THR A	75	34.853	42.777	29.988	1.00	6.37	6
ATOM	611	CE	THR A	75	35.716	41.696	29.687	1.00	6.28	6
ATOM	612	CE	THR A	75	35.677	42.916	29.589	1.00	6.45	6
ATOM	613	CZ	THR A	75	35.547	41.855	27.414	1.00	6.14	6
ATOM	614	CZ	THR A	75	36.039	41.257	28.570	1.00	6.25	6
ATOM	615	C	THR A	75	35.113	40.195	28.479	1.00	6.33	8
ATOM	616	O	THR A	75	35.113	40.195	28.479	1.00	6.33	8
ATOM	617	N	THR A	75	32.274	47.302	27.713	1.00	7.91	7
ATOM	618	CA	GLY A	76	33.355	48.068	29.555	1.00	7.27	6
ATOM	619	CA	GLY A	76	32.468	49.243	29.681	1.00	7.13	6
ATOM	620	CA	GLY A	76	32.204	49.486	31.152	1.00	7.13	6
ATOM	621	C	GLY A	76	32.561	48.904	32.048	1.00	6.91	8
ATOM	622	CA	THR A	77	30.855	50.469	32.813	1.00	7.25	7
ATOM	623	CB	THR A	77	30.386	52.172	32.914	1.00	7.64	6
ATOM	624	CG	THR A	77	29.223	52.337	32.073	1.00	8.21	8
ATOM	625	CG	THR A	77	31.378	53.173	32.361	1.00	7.62	6
ATOM	626	HN1	THR A	77	28.942	49.627	33.304	1.00	7.62	6
ATOM	627	HN2	THR A	77	28.942	49.627	33.304	1.00	7.62	6
ATOM	628	N	LYS A	78	29.460	49.853	34.613	1.00	7.39	8
ATOM	629	CA	LYS A	78	28.398	49.084	36.759	1.00	8.24	7
ATOM	630	CB	LYS A	78	28.465	49.384	35.751	1.00	8.67	6
ATOM	631	CG	LYS A	78	27.459	48.604	37.551	1.00	11.52	6
ATOM	632	CG	LYS A	78	27.582	49.117	39.004	1.00	13.82	6
ATOM	633	CZ	LYS A	78	26.112	48.228	39.824	1.00	15.45	6
ATOM	634	H2	LYS A	78	26.112	48.228	39.824	1.00	15.45	6
ATOM	635	O	LYS A	78	27.022	49.428	34.735	1.00	18.78	7
ATOM	636	O	LYS A	78	26.165	48.565	34.477	1.00	8.67	8

A10H	637	N	SER	A	79	26	719	50	759	34	578	1	0	9	31	7	
A10H	638	CA	SER	A	79	25	001	51	161	34	086	1	0	0	12	6	
A10H	639	CB	SER	A	79	25	100	52	607	34	300	1	0	10	15	8	
A10H	640	CG	SER	A	79	25	960	53	338	33	485	1	0	10	18	6	
A10H	641	C	SER	A	79	25	262	50	703	32	644	1	0	0	9	7	
A10H	642	C	SER	A	79	24	162	50	254	32	312	1	0	10	15	8	
A10H	643	CA	GLU	A	80	25	001	50	525	30	145	1	0	0	9	3	
A10H	644	CB	GLU	A	80	25	001	50	525	30	145	1	0	0	9	3	
A10H	645	CG	GLU	A	80	27	629	50	452	29	723	1	0	10	10	4	
A10H	646	CA	GLU	B	80	27	564	51	928	29	768	1	0	11	5	4	
A10H	647	CG	GLU	B	80	26	902	52	167	26	769	1	0	14	3	6	
A10H	648	DE	GLU	A	80	26	881	51	408	28	913	1	0	15	2	8	
A10H	649	DE	GLU	A	80	25	983	53	186	27	075	1	0	10	12	8	
A10H	650	CA	GLU	B	81	25	001	50	525	30	145	1	0	0	9	3	
A10H	651	C	GLU	B	81	25	005	48	179	29	720	1	0	10	8	7	
A10H	652	H	LEU	A	81	26	441	47	873	31	394	1	0	0	9	0	
A10H	653	CA	LEU	A	81	26	155	46	428	31	531	1	0	0	12	6	
A10H	654	CB	LEU	A	81	27	180	45	716	32	385	1	0	8	2	4	
A10H	655	CG	LEU	A	81	26	966	44	272	32	863	1	0	0	9	8	
A10H	656	CA	LEU	B	81	27	083	43	644	31	740	1	0	0	9	6	
A10H	657	CG	LEU	B	81	27	083	43	644	31	740	1	0	0	9	6	
A10H	658	C	LEU	B	81	24	710	46	226	32	053	1	0	0	9	4	
A10H	659	C	LEU	A	81	23	952	45	386	31	515	1	0	0	8	9	
A10H	660	N	GLM	A	82	24	247	47	003	33	042	1	0	0	9	3	
A10H	661	CA	GLM	A	82	22	053	46	834	33	479	1	0	0	8	1	
A10H	662	CB	GLM	A	82	22	388	47	739	34	681	1	0	10	1	5	
A10H	663	CG	GLM	A	82	23	390	47	739	34	681	1	0	10	1	5	
A10H	664	C	GLM	A	82	22	390	47	739	34	681	1	0	10	1	5	
A10H	665	DE	GLM	A	82	23	497	49	180	36	990	1	0	0	15	7	
A10H	666	WE	Z	GLM	A	82	22	947	47	380	38	266	1	0	14	0	
A10H	667	C	GLM	A	82	21	876	47	108	32	358	1	0	10	18	6	
A10H	668	C	GLM	A	82	20	854	46	455	32	247	1	0	10	13	8	
A10H	669	N	ASP	A	83	22	106	48	088	31	501	1	0	10	15	8	
A10H	670	CA	ASP	A	83	21	351	49	615	29	514	1	0	0	10	3	
A10H	671	CB	ASP	A	83	21	351	49	615	29	514	1	0	0	10	3	
A10H	672	CG	ASP	A	83	21	228	50	893	30	246	1	0	18	19	6	
A10H	673	CO	ASP	A	83	20	404	50	950	31	175	1	0	10	15	9	
A10H	674	OE	ASP	A	83	21	832	51	94	29	841	1	0	22	13	8	
A10H	675	C	ASP	A	83	21	439	47	203	29	307	1	0	10	0	8	
A10H	676	C	ASP	A	83	20	393	46	942	28	751	1	0	10	1	0	
A10H	677	CA	ASP	A	83	20	393	46	942	28	751	1	0	10	1	0	
A10H	678	CB	ALA	B	84	22	530	45	64	28	120	1	0	10	13	2	
A10H	679	CB	ALA	B	84	24	057	45	019	27	847	1	0	0	7	4	
A10H	680	C	ALA	B	84	21	758	44	332	28	688	1	0	10	10	4	
A10H	681	C	ALA	B	84	20	980	43	692	27	939	1	0	10	13	2	
A10H	682	N	ILE	A	85	21	820	44	045	29	995	1	0	10	14	7	
A10H	683	CA	ILE	A	85	21	501	43	165	28	104	1	0	10	10	4	
A10H	684	CB	ILE	A	85	21	501	43	165	28	104	1	0	10	10	4	
A10H	685	CG	ILE	A	85	20	474	41	875	32	906	1	0	0	6	0	
A10H	686	CO	ILE	A	85	22	921	42	132	32	080	1	0	10	9	1	
A10H	687	CO	ILE	A	85	23	684	42	092	33	399	1	0	10	12	6	
A10H	688	C	ILE	A	85	19	543	43	282	30	566	1	0	10	10	5	
A10H	689	C	ILE	A	85	18	768	42	340	30	313	1	0	10	14	1	
A10H	690	N	GLY	A	86	19	100	44	530	30	752	1	0	10	11	9	
A10H	691	CA	GLY	A	86	17	169	44	837	30	461	1	0	10	11	7	
A10H	692	C	GLY	A	86	17	181	44	828	29	181	1	0	10	12	1	
A10H	693	CB	SER	A	87	16	109	44	068	28	922	1	0	10	12	8	
A10H	694	H	SER	A	87	17	881	45	049	28	130	1	0	10	12	3	
A10H	695	CA	SER	A	87	17	451	44	776	26	770	1	0	10	12	9	
A10H	696	CB	SER	A	87	18	310	45	749	25	742	1	0	10	13	9	
A10H	697	CG	SER	A	87	18	310	45	749	25	742	1	0	10	13	9	
A10H	698	C	SER	A	87	17	310	43	266	26	445	1	0	10	12	6	
A10H	699	C	SER	A	87	16	395	42	812	25	776	1	0	10	12	4	
A10H	700	H	LEU	A	88	18	262	42	859	26	956	1	0	10	12	9	
A10H	701	CA	LEU	A	88	18	199	41	020	26	764	1	0	10	12	3	
A10H	702	CB	LEU	A	88	18	199	41	020	26	764	1	0	10	12	3	
A10H	703	CG	LEU	A	88	18	199	41	020	26	764	1	0	10	12	3	
A10H	704	CO	LEU	A	88	21	896	40	046	27	197	1	0	10	8	6	
A10H	705	CO	LEU	A	88	20	566	39	947	25	036	1	0	10	11	9	
A10H	706	C	LEU	A	88	16	995	40	443	27	507	1	0	10	12	3	
A10H	707	C	LEU	A	88	16	238	39	575	26	993	1	0	10	12	9	
A10H	708	H	MIS	A	89	16	784	40	866	28	752	1	0	10	11	7	
A10H	709	CA	MIS	A	89	15	713	40	761	28	507	1	0	10	12	3	
A10H	710	CB	MIS	A	89	15	713	40	761	28	507	1	0	10	12	3	
A10H	711	CG	MIS	A	89	16	594	39	915	31	863	1	0	10	11	6	
A10H	712	CG	MIS	A	89	16	594	39	915	31	863	1	0	10	11	6	
A10H	713	HE	MIS	A	89	17	107	40	353	33	037	1	0	10	10	3	
A10H	714	HE	MIS	A	89	17	865	39	425	33	593	1	0	10	10	8	
A10H	715	HE	MIS	A	89	17	337	38	343	32	823	1	0	10	11	6	
A10H	716	C	MIS	A	89	15	178	40	781	28	538	1	0	10	13	6	
A10H	717	C	MIS	A	89	15	178	40	781	28	538	1	0	10	13	6	
A10H	718	CA	SER	A	90	15	225	41	950	28	265	1	0	10	15	7	
A10H	719	H	SER	A	90	12	957	42	281	27	645	1	0	10	15	9	
A10H	720	CB	SER	A	90	12	784	43	796	27	638	1	0	10	16	6	
A10H	721	CG	SER	A	90	13	761	44	225	26	518	1	0	10	19	7	
A10H	722	C	SER	A	90	10	112	41	472	26	411	1	0	10	15	9	
A10H	723	C	SER	A	90	12	412	41	428	25	924	1	0	10	15	8	
A10H	724	CA	ARG	A	91	13	632	40	675	25	854	1	0	10	16	5	
A10H	725	CB	ARG	A	91	13	632	40	675	25	854	1	0	10	16	5	
A10H	726	CB	ARG	A	91	14	651	39	910	23	489	1	0	10	17	9	
A10H	727	CG	ARG	A	91	14	977	41	395	23	476	1	0	10	23	9	
A10H	728	CG	ARG	A	91	14	977	41	395	23	476	1	0	10	23	9	
A10H	729	HE	ARG	A	91	15	409	43	230	22	020	1	0	10	31	45	
A10H	730	CZ	ARG	A	91	15	007	44	382	22	298	1	0	10	33	9	
A10H	731	CZ	ARG	A	91	15	007	44	382	22	298	1	0	10	33	9	
A10H	732	WE	Z	ARG	A	91	13	433	44	587	23	121	1	0	10	33	4
A10H	733	WE	Z	ARG	A	91	13	433	44	587	23	121	1	0	10	33	4
A10H	734	O	ARG	A	91	13	596	38	364	25	152	1	0	10	14	3	
A10H	735	O	ARG	A	91	13	627	37	473	24	354	1	0	10	17	9	
A10H	736	CA	ASN	A	92	13	435	38	126	26	487	1	0	10	19	4	
A10H	737	CB	ASN	A	92	13	435	38	126	26	487	1	0	10	19	4	
A10H	738	CB	ASN	A	92	13	435	38	126	26	487	1	0	10	19	4	
A10H	739	CO	ASN	A	92	12	229	35	993	26							

243	N	VAL	A	93	15.886	36.642	26.989	1.00	16.55	7
244	CA	VAL	A	93	17.213	36.038	26.833	1.00	15.28	6
245	CA	VAL	A	93	18.120	36.688	25.785	1.00	12.97	6
246	CE1	VAL	A	93	19.467	36.021	25.899	1.00	11.55	6
247	CE2	VAL	A	93	17.771	36.161	25.584	1.00	10.40	6
248	G	VAL	A	93	17.771	36.161	25.584	1.00	10.40	6
249	G	VAL	A	93	17.736	37.228	28.829	1.00	14.36	7
250	N	VAL	A	94	18.211	35.927	28.742	1.00	13.97	7
251	CA	VAL	A	94	18.792	34.812	30.045	1.00	13.10	6
252	CA	VAL	A	94	18.642	33.375	30.542	1.00	13.62	6
253	CE1	VAL	A	94	17.065	33.483	30.193	1.00	19.51	6
254	CE2	VAL	A	94	17.065	33.483	30.193	1.00	19.51	6
255	DE1	VAL	A	94	17.710	30.855	31.198	1.00	21.76	8
256	DE2	VAL	A	94	16.205	31.683	32.559	1.00	21.21	7
257	G	VAL	A	94	20.275	35.223	30.003	1.00	12.28	6
258	G	VAL	A	94	20.882	35.211	28.935	1.00	12.02	9
259	N	VAL	A	95	22.115	34.030	31.272	1.00	10.46	6
260	CA	VAL	A	95	22.115	34.030	31.272	1.00	10.46	6
261	CE1	VAL	A	95	22.215	37.553	31.568	1.00	11.92	6
262	CE2	VAL	A	95	23.646	38.014	31.735	1.00	12.03	6
263	CE3	VAL	A	95	21.591	38.367	30.411	1.00	12.21	6
264	G	VAL	A	95	22.942	35.269	32.302	1.00	9.65	6
265	G	VAL	A	95	22.942	35.269	32.302	1.00	9.65	6
266	CA	VAL	A	96	24.920	33.423	32.853	1.00	8.40	7
267	CA	VAL	A	96	24.920	33.423	32.853	1.00	8.40	7
268	CE1	VAL	A	96	25.217	32.512	32.267	1.00	8.31	6
269	CE2	VAL	A	96	24.055	31.583	31.987	1.00	8.37	6
270	CE3	VAL	A	96	24.298	30.500	31.130	1.00	8.46	6
271	CE4	VAL	A	96	24.298	30.500	31.130	1.00	8.46	6
272	CE5	VAL	A	96	22.797	31.752	32.651	1.00	8.19	6
273	CE6	VAL	A	96	22.797	31.752	32.651	1.00	8.19	6
274	CE7	VAL	A	96	22.011	29.854	32.186	1.00	8.05	6
275	CE8	VAL	A	96	21.055	28.640	31.004	1.00	7.64	8
276	CE9	VAL	A	96	26.218	34.655	33.000	1.00	8.00	6
277	CE10	VAL	A	96	26.032	34.655	32.955	1.00	7.99	7
278	CE11	VAL	A	96	26.032	34.655	32.955	1.00	7.99	7
279	CE12	VAL	A	96	27.818	35.621	34.578	1.00	7.66	6
280	G	VAL	A	97	29.038	34.754	34.756	1.00	7.84	6
281	G	VAL	A	97	28.950	33.655	35.307	1.00	7.51	8
282	N	ASP	A	98	30.194	35.231	34.285	1.00	7.87	7
283	CA	ASP	A	98	31.455	34.489	34.482	1.00	7.94	6
284	CA	ASP	A	98	31.455	34.489	34.482	1.00	7.94	6
285	CE1	ASP	A	98	33.432	33.828	33.077	1.00	7.60	6
286	CE2	ASP	A	98	33.916	33.085	33.920	1.00	8.28	8
287	CE3	ASP	A	98	33.791	33.741	31.896	1.00	7.14	8
288	CE4	ASP	A	98	31.868	34.668	35.953	1.00	7.80	6
289	CE5	ASP	A	98	32.535	34.745	36.108	1.00	7.83	7
290	CE6	ASP	A	98	32.535	34.745	36.108	1.00	7.83	7
291	CE7	ASP	A	99	32.708	33.576	38.035	1.00	7.25	6
292	CE8	ASP	A	99	31.742	32.582	38.791	1.00	8.70	6
293	CE9	ASP	A	99	32.193	32.386	40.195	1.00	9.79	6
294	CE10	ASP	A	99	30.366	33.362	38.885	1.00	9.90	6
295	CE11	ASP	A	99	34.155	33.123	38.148	1.00	6.81	6
296	N	VAL	A	99	34.461	31.987	37.850	1.00	6.46	8
297	CA	VAL	A	99	35.082	34.017	38.489	1.00	6.60	7
298	CA	VAL	A	99	36.437	33.766	38.596	1.00	6.45	6
299	CE1	VAL	A	99	36.773	34.108	37.497	1.00	6.99	6
300	CE2	VAL	A	99	36.773	34.108	37.497	1.00	6.99	6
301	CE3	VAL	A	99	36.920	33.003	40.041	1.00	6.94	6
302	CE4	VAL	A	99	37.306	34.866	40.566	1.00	6.72	8
303	CE5	VAL	A	99	36.882	32.651	40.723	1.00	6.41	7
304	CE6	VAL	A	99	37.189	32.337	42.133	1.00	7.10	6
305	CE7	VAL	A	99	36.853	32.749	42.645	1.00	6.90	6
306	CE8	VAL	A	99	33.653	32.749	42.645	1.00	6.90	6
307	CE9	VAL	A	99	33.653	31.509	43.300	1.00	9.60	6
308	CE10	VAL	A	99	34.726	33.873	43.244	1.00	7.63	6
309	CE11	VAL	A	99	38.456	31.883	42.579	1.00	5.96	6
310	CE12	VAL	A	99	39.672	31.746	43.182	1.00	6.92	8
311	CE13	VAL	A	99	40.471	30.249	42.025	1.00	5.58	6
312	CE14	VAL	A	99	40.963	29.889	40.727	1.00	5.08	6
313	CE15	VAL	A	99	42.327	29.247	40.912	1.00	5.00	6
314	CE16	VAL	A	99	42.309	28.218	41.608	1.00	5.00	8
315	CE17	VAL	A	99	43.493	29.233	41.442	1.00	5.00	7
316	CE18	VAL	A	99	43.490	31.165	41.560	1.00	5.69	6
317	CE19	VAL	A	99	42.261	31.165	41.560	1.00	5.69	6
318	CE20	VAL	A	99	41.853	32.270	42.103	1.00	5.60	7
319	CE21	VAL	A	99	42.935	33.520	42.506	1.00	5.59	6
320	CE22	VAL	A	99	44.089	33.287	41.487	1.00	6.54	6
321	CE23	VAL	A	99	43.645	33.442	40.043	1.00	7.70	6
322	CE24	VAL	A	99	43.580	34.512	39.230	1.00	6.52	6
323	CE25	VAL	A	99	42.794	32.769	38.082	1.00	8.00	7
324	CE26	VAL	A	99	42.993	34.113	38.070	1.00	8.31	7
325	CE27	VAL	A	99	42.555	34.977	42.419	1.00	5.57	6
326	CE28	VAL	A	99	41.470	35.229	41.899	1.00	5.20	8
327	CE29	VAL	A	99	43.438	35.861	42.914	1.00	5.83	7
328	CE30	VAL	A	99	43.626	37.313	42.871	1.00	6.01	6
329	CE31	VAL	A	99	42.528	37.393	44.978	1.00	8.59	6
330	CE32	VAL	A	99	41.768	37.393	44.978	1.00	8.59	6
331	CE33	VAL	A	99	41.373	38.324	46.133	1.00	9.80	6
332	CE34	VAL	A	99	40.973	39.748	45.746	1.00	8.97	6
333	CE35	VAL	A	99	39.514	39.723	45.383	1.00	8.50	7
334	CE36	VAL	A	99	44.489	37.894	42.278	1.00	6.11	6
335	CE37	VAL	A	99	44.501	37.894	42.278	1.00	6.11	6
336	CE38	VAL	A	99	44.501	37.894	42.278	1.00	6.11	6
337	CE39	VAL	A	99	45.699	39.429	40.846	1.00	6.18	6
338	CE40	VAL	A	99	45.660	39.063	39.341	1.00	5.88	6
339	CE41	VAL	A	99	45.785	40.943	41.101	1.00	6.37	6
340	CE42	VAL	A	99	44.781	41.578	41.199	1.00	6.24	8
341	CE43	VAL	A	99	47.004	43.001	42.573	1.00	7.01	6
342	CE44	VAL	A	99	47.004	43.001	42.573	1.00	7.01	6
343	CE45	VAL	A	99	46.524	44.726	42.659	1.00	6.76	8
344	CE46	VAL	A	99	47.489	42.945	43.637	1.00	7.49	7



ATOM	955	CG	ASN	A 122	54.009	15.047	44.180	1.00	13.39	6
ATOM	956	CG	ASN	A 122	51.085	15.591	44.766	1.00	13.50	8
ATOM	957	CG	ASN	A 122	51.111	18.023	44.712	1.00	16.22	8
ATOM	958	CG	ASN	A 122	51.911	18.023	44.712	1.00	16.22	8
ATOM	959	CG	ASN	A 122	54.881	18.130	44.566	1.00	9.02	8
ATOM	960	N	ARG	A 123	52.869	18.855	43.722	1.00	9.27	6
ATOM	961	CA	ARG	A 123	52.764	19.983	44.484	1.00	9.27	6
ATOM	962	CG	ARG	A 123	51.675	20.969	44.227	1.00	7.86	6
ATOM	963	CG	ARG	A 123	52.047	21.786	42.991	1.00	6.67	6
ATOM	964	CG	ARG	A 123	51.739	21.959	40.404	1.00	9.23	7
ATOM	965	HE	ARG	A 123	51.739	21.959	40.404	1.00	9.23	7
ATOM	966	CG	ARG	A 123	50.906	22.373	40.275	1.00	10.25	6
ATOM	967	HE	ARG	A 123	49.828	23.054	41.044	1.00	9.79	7
ATOM	968	CG	ARG	A 123	51.000	23.793	39.273	1.00	10.20	7
ATOM	969	CG	ARG	A 123	52.622	20.374	42.985	1.00	8.21	8
ATOM	970	N	ARG	A 123	52.622	20.374	42.985	1.00	8.21	8
ATOM	971	N	ASN	A 124	52.406	18.256	46.379	1.00	9.56	7
ATOM	972	CA	ASN	A 124	52.351	17.705	47.102	1.00	10.31	6
ATOM	973	CG	ASN	A 124	51.742	16.299	47.800	1.00	11.34	6
ATOM	974	CG	ASN	A 124	50.275	16.347	47.495	1.00	14.21	6
ATOM	975	CG	ASN	A 124	49.883	15.351	44.580	1.00	10.42	9
ATOM	976	CG	ASN	A 124	49.883	15.351	44.580	1.00	10.42	9
ATOM	977	CG	ASN	A 124	53.796	17.564	46.237	1.00	10.74	6
ATOM	978	N	ASN	A 124	53.926	17.342	47.439	1.00	10.85	6
ATOM	979	N	GLN	A 125	54.872	17.660	47.925	1.00	11.21	6
ATOM	980	CA	GLN	A 125	56.223	17.569	47.925	1.00	11.21	6
ATOM	981	CG	GLN	A 125	57.199	16.823	45.919	1.00	9.50	6
ATOM	982	CG	GLN	A 125	57.199	16.823	45.919	1.00	9.50	6
ATOM	983	CG	GLN	A 125	59.546	16.199	46.402	1.00	8.01	6
ATOM	984	CG	GLN	A 125	59.184	16.310	46.208	1.00	6.56	8
ATOM	985	HE	GLN	A 125	60.762	15.784	46.738	1.00	6.20	7
ATOM	986	CG	GLN	A 125	56.871	18.915	48.156	1.00	11.48	8
ATOM	987	CG	GLN	A 125	56.900	19.997	47.146	1.00	11.44	8
ATOM	988	N	GLU	A 126	53.345	19.440	49.100	1.00	12.64	7
ATOM	989	CA	GLU	A 126	58.053	20.468	49.100	1.00	12.64	7
ATOM	990	CG	GLU	A 126	58.042	20.856	51.115	1.00	11.31	6
ATOM	991	CG	GLU	A 126	56.589	20.799	51.582	1.00	12.45	6
ATOM	992	CG	GLU	A 126	56.371	21.288	52.993	1.00	13.36	6
ATOM	993	CG	GLU	A 126	57.329	21.471	53.748	1.00	13.22	8
ATOM	994	CG	GLU	A 126	59.515	20.293	49.195	1.00	11.72	8
ATOM	995	CG	GLU	A 126	59.515	20.293	49.195	1.00	11.72	8
ATOM	996	N	THR	A 127	60.198	19.292	49.513	1.00	12.98	8
ATOM	997	CA	THR	A 127	60.045	21.216	48.430	1.00	14.11	8
ATOM	998	CG	THR	A 127	61.407	21.048	47.954	1.00	15.19	6
ATOM	999	CG	THR	A 127	61.937	21.193	48.420	1.00	14.68	6
ATOM	1000	CG	THR	A 127	61.937	21.193	48.420	1.00	14.68	6
ATOM	1001	CG	THR	A 127	60.902	19.993	45.774	1.00	15.31	8
ATOM	1002	CG	THR	A 127	62.377	21.925	48.614	1.00	16.26	6
ATOM	1003	N	THR	A 127	62.552	21.851	48.283	1.00	16.67	8
ATOM	1004	N	THR	A 127	62.015	22.892	49.100	1.00	16.75	7
ATOM	1005	CA	SER	A 128	63.000	23.747	50.125	1.00	17.24	6
ATOM	1006	CG	SER	A 128	61.875	25.859	49.935	1.00	15.04	6
ATOM	1007	CG	SER	A 128	61.875	25.859	49.935	1.00	15.04	6
ATOM	1008	CG	SER	A 128	61.875	25.859	49.935	1.00	15.04	6
ATOM	1009	CG	SER	A 128	61.875	25.859	49.935	1.00	15.04	6
ATOM	1010	CG	SER	A 128	61.875	25.859	49.935	1.00	15.04	6
ATOM	1011	CG	SER	A 128	61.875	25.859	49.935	1.00	15.04	6
ATOM	1012	CG	SER	A 128	61.875	25.859	49.935	1.00	15.04	6
ATOM	1013	CG	SER	A 128	61.875	25.859	49.935	1.00	15.04	6
ATOM	1014	CG	SER	A 128	61.875	25.859	49.935	1.00	15.04	6
ATOM	1015	CG	SER	A 128	61.875	25.859	49.935	1.00	15.04	6
ATOM	1016	CG	SER	A 128	61.875	25.859	49.935	1.00	15.04	6
ATOM	1017	CG	SER	A 128	61.875	25.859	49.935	1.00	15.04	6
ATOM	1018	CG	SER	A 128	61.875	25.859	49.935	1.00	15.04	6
ATOM	1019	CG	SER	A 128	61.875	25.859	49.935	1.00	15.04	6
ATOM	1020	CG	SER	A 128	61.875	25.859	49.935	1.00	15.04	6
ATOM	1021	CG	SER	A 128	61.875	25.859	49.935	1.00	15.04	6
ATOM	1022	CG	SER	A 128	61.875	25.859	49.935	1.00	15.04	6
ATOM	1023	CG	SER	A 128	61.875	25.859	49.935	1.00	15.04	6
ATOM	1024	CG	SER	A 128	61.875	25.859	49.935	1.00	15.04	6
ATOM	1025	CG	SER	A 128	61.875	25.859	49.935	1.00	15.04	6
ATOM	1026	CG	SER	A 128	61.875	25.859	49.935	1.00	15.04	6
ATOM	1027	CG	SER	A 128	61.875	25.859	49.935	1.00	15.04	6
ATOM	1028	CG	SER	A 128	61.875	25.859	49.935	1.00	15.04	6
ATOM	1029	CG	SER	A 128	61.875	25.859	49.935	1.00	15.04	6
ATOM	1030	CG	SER	A 128	61.875	25.859	49.935	1.00	15.04	6
ATOM	1031	CG	SER	A 128	61.875	25.859	49.935	1.00	15.04	6
ATOM	1032	CG	SER	A 128	61.875	25.859	49.935	1.00	15.04	6
ATOM	1033	CG	SER	A 128	61.875	25.859	49.935	1.00	15.04	6
ATOM	1034	CG	SER	A 128	61.875	25.859	49.935	1.00	15.04	6
ATOM	1035	CG	SER	A 128	61.875	25.859	49.935	1.00	15.04	6
ATOM	1036	CG	SER	A 128	61.875	25.859	49.935	1.00	15.04	6
ATOM	1037	CG	SER	A 128	61.875	25.859	49.935	1.00	15.04	6
ATOM	1038	CG	SER	A 128	61.875	25.859	49.935	1.00	15.04	6
ATOM	1039	CG	SER	A 128	61.875	25.859	49.935	1.00	15.04	6
ATOM	1040	CG	SER	A 128	61.875	25.859	49.935	1.00	15.04	6
ATOM	1041	CG	SER	A 128	61.875	25.859	49.935	1.00	15.04	6
ATOM	1042	CG	SER	A 128	61.875	25.859	49.935	1.00	15.04	6
ATOM	1043	CG	SER	A 128	61.875	25.859	49.935	1.00	15.04	6
ATOM	1044	CG	SER	A 128	61.875	25.859	49.935	1.00	15.04	6
ATOM	1045	CG	SER	A 128	61.875	25.859	49.935	1.00	15.04	6
ATOM	1046	CG	SER	A 128	61.875	25.859	49.935	1.00	15.04	6
ATOM	1047	CG	SER	A 128	61.875	25.859	49.935	1.00	15.04	6
ATOM	1048	CG	SER	A 128	61.875	25.859	49.935	1.00	15.04	6
ATOM	1049	CG	SER	A 128	61.875	25.859	49.935	1.00	15.04	6
ATOM	1050	CG	SER	A 128	61.875	25.859	49.935	1.00	15.04	6
ATOM	1051	CG	SER	A 128	61.875	25.859	49.935	1.00	15.04	6
ATOM	1052	CG	SER	A 128	61.875	25.859	49.935	1.00	15.04	6
ATOM	1053	CG	SER	A 128	61.875	25.859	49.935	1.00	15.04	6
ATOM	1054	CG	SER	A 128	61.875	25.859	49.935	1.00	15.04	6
ATOM	1055	CG	SER	A 128	61.875	25.859	49.935	1.00	15.04	6
ATOM	1056	CG	SER	A 128	61.875	25.859	49.935	1.00	15.04	6
ATOM	1057	CG	SER	A 128	61.875	25.859	49.935	1.00	15.04	6
ATOM	1058	CG	SER	A 128	61.875	25.859	49.935	1.00	15.04	6
ATOM	1059	CG	SER	A 128	61.875	25.859	49.935	1.00	15.04	6
ATOM	1060	CG	SER	A 128	61.875	25.859	49.935	1.00	15.04	6

1061	CD	LVS A 134	59.998	42.325	50.294	1.00	19.11	6
1062	CE	LVS A 134	59.652	43.476	51.253	1.00	22.55	7
1063	RE	LVS A 134	59.315	44.566	51.920	1.00	25.91	7
1064	TRP A 134	59.066	45.661	52.587	1.00	29.26	7	
1065	0	LVS A 134	57.075	38.997	47.439	1.00	10.75	6
1066	0	LVS A 135	55.444	38.754	48.393	1.00	10.72	8
1067	CB	ALA A 135	54.411	38.356	48.046	1.00	9.82	6
1068	CB	ALA A 135	53.713	37.071	48.552	1.00	8.45	6
1069	0	ALA A 135	53.360	39.428	47.848	1.00	9.62	6
1070	0	ALA A 135	52.716	39.452	46.812	1.00	9.28	7
1071	0	TRP A 135	52.716	39.452	46.812	1.00	9.28	7
1072	CB	TRP A 136	51.676	40.473	46.354	1.00	8.76	6
1073	CB	TRP A 136	51.683	40.690	44.866	1.00	9.45	6
1074	CE	TRP A 136	52.918	41.438	44.430	1.00	12.31	6
1075	CE	TRP A 136	53.308	42.981	44.428	1.00	12.31	6
1076	CE	TRP A 136	53.308	42.981	44.428	1.00	12.31	6
1077	CE	TRP A 136	52.224	43.924	44.799	1.00	11.71	6
1078	CE	TRP A 136	54.099	40.924	43.934	1.00	13.83	6
1079	HE	TRP A 136	54.954	41.951	43.599	1.00	15.49	7
1080	C2	TRP A 136	54.846	44.456	43.772	1.00	14.17	6
1081	C2	TRP A 136	52.680	45.213	44.627	1.00	12.36	6
1082	CE	TRP A 136	50.351	37.517	42.521	1.00	8.10	6
1083	CE	TRP A 136	50.351	37.517	42.521	1.00	8.10	6
1084	0	TRP A 136	49.535	39.452	46.064	1.00	8.39	8
1085	0	TRP A 137	50.028	40.192	48.084	1.00	8.12	7
1086	CA	TRP A 137	48.844	39.707	48.761	1.00	7.75	6
1087	CA	TRP A 137	49.275	38.704	49.884	1.00	7.93	6
1088	CE	TRP A 137	50.351	37.517	42.521	1.00	8.10	6
1089	CE	TRP A 137	50.351	37.517	42.521	1.00	8.10	6
1090	0	TRP A 137	48.960	40.772	49.490	1.00	7.59	6
1091	0	TRP A 137	47.063	40.370	50.112	1.00	7.09	8
1092	0	TRP A 138	48.425	42.026	49.486	1.00	7.55	7
1093	CA	ASP A 138	47.680	43.038	50.223	1.00	7.91	6
1094	CA	ASP A 138	48.667	44.060	50.793	1.00	10.36	6
1095	CA	ASP A 138	48.667	44.060	50.793	1.00	10.36	6
1096	0	TRP A 138	46.820	45.294	51.881	1.00	16.48	6
1097	0	TRP A 138	48.865	45.781	52.416	1.00	16.18	8
1098	0	TRP A 138	46.627	43.671	49.316	1.00	7.07	8
1099	0	TRP A 138	47.039	44.379	48.405	1.00	7.97	8
1100	0	TRP A 139	45.334	43.627	49.220	1.00	6.44	7
1101	0	TRP A 139	43.394	43.011	47.964	1.00	7.03	6
1102	CE	PHE A 139	43.394	43.011	47.964	1.00	7.03	6
1103	CE	PHE A 139	44.078	42.176	46.892	1.00	8.72	6
1104	CE	PHE A 139	44.948	41.138	47.287	1.00	7.30	6
1105	CE	PHE A 139	43.835	42.398	45.538	1.00	7.95	6
1106	CE	PHE A 139	42.600	43.358	46.350	1.00	8.46	6
1107	CE	PHE A 139	43.394	43.011	47.964	1.00	7.03	6
1108	CE	PHE A 139	43.394	43.011	47.964	1.00	7.03	6
1109	0	PHE A 139	43.461	44.987	49.487	1.00	9.73	6
1110	0	PHE A 139	42.707	44.536	50.343	1.00	9.71	8
1111	0	PHE A 140	43.599	46.294	49.178	1.00	10.52	7
1112	0	PHE A 140	42.823	47.266	49.985	1.00	11.46	6
1113	0	PHE A 140	41.067	48.263	50.745	1.00	17.79	6
1114	0	PHE A 140	45.059	48.594	50.380	1.00	22.49	6
1115	0	PHE A 140	47.197	48.785	51.626	1.00	25.79	6
1116	0	PHE A 140	46.477	48.985	51.487	1.00	32.35	7
1117	0	PHE A 140	48.873	49.714	52.529	1.00	34.62	7
1118	0	PHE A 140	49.440	48.518	52.321	1.00	34.86	7
1119	0	PHE A 140	41.766	48.037	49.205	1.00	11.28	6
1120	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1121	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1122	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1123	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1124	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1125	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1126	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1127	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1128	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1129	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1130	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1131	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1132	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1133	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1134	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1135	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1136	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1137	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1138	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1139	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1140	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1141	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1142	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1143	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1144	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1145	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1146	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1147	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1148	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1149	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1150	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1151	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1152	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1153	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1154	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1155	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1156	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1157	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1158	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1159	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1160	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1161	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1162	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1163	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1164	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1165	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1166	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1167	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1168	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1169	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1170	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1171	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1172	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1173	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1174	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1175	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1176	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1177	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1178	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1179	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1180	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1181	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1182	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1183	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1184	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1185	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1186	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1187	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1188	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1189	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1190	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1191	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1192	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1193	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1194	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1195	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1196	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1197	0	PHE A 140	40.965	48.099	49.916	1.00	11.54	8
1198	0	PHE A 140	40.965	48.099	49.9			

AIHM	1167	H	THH	A 127	32,491	50,454	50,175	1,00	11,640	7
AIHM	1168	CA	THH	A 127	31,200	50,151	49,487	1,00	11,226	6
AIHM	1169	CA	THH	A 127	31,164	51,128	48,161	1,00	11,415	6
AIHM	1170	CG1	THH	A 127	31,769	52,465	48,360	1,00	11,122	8
AIHM	1171	CG2	THH	A 127	29,782	51,325	47,548	1,00	9,27	6
AIHM	1172	C	THH	A 127	30,895	48,884	49,247	1,00	11,00	6
AIHM	1173	C	THH	A 127	29,771	48,330	49,642	1,00	10,101	7
AIHM	1174	CA	THH	A 127	29,771	48,330	49,642	1,00	10,101	7
AIHM	1175	CA	THH	A 127	29,245	47,866	49,538	1,00	10,34	6
AIHM	1176	CA	THH	A 127	29,308	46,555	48,117	1,00	10,35	6
AIHM	1177	CG	THH	A 127	28,798	47,328	46,967	1,00	9,97	6
AIHM	1178	CG1	THH	A 127	29,669	47,030	46,916	1,00	9,49	6
AIHM	1179	CG2	THH	A 127	27,474	46,443	46,915	1,00	9,71	6
AIHM	1180	CA	THH	A 127	27,474	46,443	46,915	1,00	9,71	6
AIHM	1181	CG2	THH	A 127	27,067	46,336	45,925	1,00	9,48	6
AIHM	1182	CG2	THH	A 127	27,067	46,314	44,844	1,00	8,99	6
AIHM	1183	CG	THH	A 127	27,441	49,705	43,833	1,00	8,37	8
AIHM	1184	CG	THH	A 127	29,940	46,030	46,026	1,00	10,22	6
AIHM	1185	C	THH	A 127	31,226	45,155	50,257	1,00	10,07	7
AIHM	1186	CA	THH	A 127	31,879	45,161	51,584	1,00	9,72	6
AIHM	1187	CA	THH	A 127	31,256	43,888	50,767	1,00	9,55	6
AIHM	1188	CG	THH	A 127	31,306	43,185	51,181	1,00	8,96	6
AIHM	1189	CG	THH	A 127	31,161	45,735	52,164	1,00	9,63	6
AIHM	1190	C	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1191	C	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1192	C	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1193	C	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1194	C	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1195	CA	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1196	CA	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1197	CG1	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1198	CG2	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1199	C	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1200	CA	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1201	CA	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1202	CG	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1203	CG	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1204	CG	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1205	CG	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1206	CG	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1207	CG	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1208	CG	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1209	CG	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1210	CG	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1211	CA	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1212	CA	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1213	CA	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1214	CG	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1215	CG	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1216	CG	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1217	CG	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1218	CG	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1219	CG	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1220	CA	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1221	CA	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1222	CG	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1223	CG	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1224	CG	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1225	CG	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1226	CG	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1227	CG	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1228	CG	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1229	CG	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1230	CG	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1231	CG	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1232	CG	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1233	CG	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1234	CG	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1235	CG	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1236	CG	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1237	CG	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1238	CG	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1239	CG	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1240	CG	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1241	CG	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1242	CG	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1243	CG	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1244	CG	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1245	CG	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1246	CG	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1247	CG	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1248	CG	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1249	CG	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1250	CG	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1251	CG	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1252	CG	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1253	CG	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1254	CG	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1255	CG	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1256	CG	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1257	CG	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1258	CG	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1259	CG	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1260	CG	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1261	CG	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1262	CG	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1263	CG	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1264	CG	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1265	CG	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1266	CG	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1267	CG	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1268	CG	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1269	CG	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1270	CG	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1271	CG	THH	A 127	31,270	45,584	53,502	1,00	9,71	7
AIHM	1272	CG	THH	A 127	31,270	45,584	53,502	1,00	9,71	7

[illegible]

A1H4	1379	C	11E	A	169	40.716	36.245	41.354	1.00	16.43	6	50.443	33.831	50.320	1.00	7.44	6
A1H4	1380	N	11E	A	170	50.806	33.446	42.742	1.00	16.39	7	52.585	33.103	49.476	1.00	6.81	6
A1H4	1381	N	11E	A	170	60.458	33.469	40.742	1.00	16.39	7	51.517	33.983	49.476	1.00	7.21	6
A1H4	1382	C	11E	A	170	59.209	32.808	40.120	1.00	16.32	6	52.567	28.942	53.875	1.00	11.49	8
A1H4	1383	C	11E	A	170	58.830	32.767	38.462	1.00	16.30	6	51.868	27.912	53.875	1.00	11.44	8
A1H4	1384	C	11E	A	170	57.519	32.181	38.067	1.00	16.28	6	53.328	28.352	54.813	1.00	11.77	7
A1H4	1385	C	11E	A	170	59.306	31.335	40.318	1.00	16.18	6	51.524	27.912	53.875	1.00	12.20	6
A1H4	1386	C	11E	A	170	58.530	30.882	41.008	1.00	15.84	7	51.524	27.912	53.875	1.00	12.20	6
A1H4	1387	C	11E	A	170	58.530	30.882	41.008	1.00	15.84	7	51.524	27.912	53.875	1.00	12.20	6
A1H4	1388	C	11E	A	170	58.504	29.492	41.954	1.00	15.28	6	55.188	26.438	56.825	1.00	15.37	6
A1H4	1389	C	11E	A	170	59.448	29.168	43.104	1.00	17.32	6	56.133	25.355	56.737	1.00	15.69	7
A1H4	1390	C	11E	A	170	60.894	29.497	43.152	1.00	19.88	6	56.118	24.277	55.962	1.00	16.02	6
A1H4	1391	C	11E	A	170	61.825	28.568	42.332	1.00	20.48	6	55.250	24.037	55.065	1.00	16.35	7
A1H4	1392	C	11E	A	170	61.825	28.568	42.332	1.00	20.48	6	55.250	24.037	55.065	1.00	16.35	7
A1H4	1393	C	11E	A	170	63.661	29.527	41.558	1.00	19.43	6	52.330	24.526	56.992	1.00	12.82	7
A1H4	1394	C	11E	A	170	63.661	29.527	41.558	1.00	19.43	6	52.330	24.526	56.992	1.00	12.82	7
A1H4	1395	C	11E	A	170	62.909	29.718	40.456	1.00	20.07	7	52.303	30.774	56.778	1.00	12.02	7
A1H4	1396	C	11E	A	170	64.884	30.070	41.101	1.00	20.59	7	51.560	28.911	57.850	1.00	13.07	7
A1H4	1397	C	11E	A	170	57.052	29.164	42.380	1.00	14.63	6	50.590	29.656	58.637	1.00	13.84	6
A1H4	1398	C	11E	A	170	56.203	30.055	42.313	1.00	14.71	6	49.736	28.715	59.449	1.00	14.51	6
A1H4	1399	C	11E	A	170	55.389	27.621	42.356	1.00	13.02	6	50.056	26.438	59.449	1.00	15.11	8
A1H4	1400	C	11E	A	170	54.752	26.357	42.862	1.00	11.93	6	47.810	26.222	60.859	1.00	14.84	6
A1H4	1401	C	11E	A	170	53.502	26.058	43.656	1.00	11.06	6	46.912	29.021	61.833	1.00	15.74	6
A1H4	1402	C	11E	A	170	54.360	26.366	43.554	1.00	11.59	6	47.575	29.715	63.000	1.00	16.47	6
A1H4	1403	C	11E	A	170	53.920	25.010	40.327	1.00	12.67	6	48.458	28.762	63.819	1.00	18.26	6
A1H4	1404	C	11E	A	170	54.175	26.058	43.656	1.00	11.59	6	48.216	27.504	63.969	1.00	19.50	8
A1H4	1405	C	11E	A	170	54.218	26.468	45.469	1.00	12.52	8	46.912	29.021	61.833	1.00	16.85	8
A1H4	1406	C	11E	A	170	55.290	26.812	45.259	1.00	11.95	7	46.912	29.021	61.833	1.00	15.32	8
A1H4	1407	C	11E	A	170	55.464	28.982	46.956	1.00	11.52	6	46.138	27.801	59.151	1.00	15.32	8
A1H4	1408	C	11E	A	170	55.813	30.424	47.326	1.00	8.63	6	47.148	26.042	60.032	1.00	14.81	7
A1H4	1409	C	11E	A	170	57.088	30.932	46.719	1.00	8.19	6	46.692	25.221	57.702	1.00	14.28	6
A1H4	1410	C	11E	A	170	56.315	30.620	45.311	1.00	8.07	6	47.709	24.968	56.979	1.00	14.54	8
A1H4	1411	C	11E	A	170	58.277	32.307	45.123	1.00	8.69	6	46.022	25.959	55.823	1.00	12.53	7
A1H4	1412	C	11E	A	170	59.512	30.949	46.686	1.00	8.72	6	46.022	25.959	55.823	1.00	12.53	7
A1H4	1413	C	11E	A	170	59.484	31.844	45.007	1.00	7.75	6	46.022	25.959	55.823	1.00	12.53	7
A1H4	1414	C	11E	A	170	54.189	28.583	47.680	1.00	11.50	6	48.425	28.409	55.816	1.00	11.89	6
A1H4	1415	C	11E	A	170	54.189	28.583	47.680	1.00	11.50	6	48.425	28.409	55.816	1.00	11.89	6
A1H4	1416	C	11E	A	170	54.257	27.496	46.252	1.00	11.28	7	47.710	28.914	54.938	1.00	9.28	6
A1H4	1417	C	11E	A	170	53.185	27.303	49.324	1.00	11.02	6	47.355	30.371	55.116	1.00	9.37	6
A1H4	1418	C	11E	A	170	53.268	25.849	49.981	1.00	7.54	6	48.277	30.683	54.339	1.00	9.60	7
A1H4	1419	C	11E	A	170	52.005	25.443	50.770	1.00	6.03	6	48.277	30.683	54.339	1.00	9.60	7
A1H4	1420	C	11E	A	170	51.880	25.947	50.993	1.00	5.90	6	47.792	23.208	53.139	1.00	10.23	6
A1H4	1421	C	11E	A	170	52.997	22.834	52.176	1.00	5.10	6	47.183	23.975	53.825	1.00	8.27	6
A1H4	1422	C	11E	A	170	53.313	28.195	50.787	1.00	5.90	6	47.183	23.975	53.825	1.00	8.27	6
A1H4	1423	C	11E	A	170	53.313	28.195	50.787	1.00	5.90	6	47.183	23.975	53.825	1.00	8.27	6
A1H4	1424	C	11E	A	170	54.402	28.117	51.068	1.00	11.32	8	47.457	22.762	50.406	1.00	8.56	6
A1H4	1425	C	11E	A	170	52.357	28.950	51.264	1.00	11.10	7	46.604	22.929	49.409	1.00	8.56	6
A1H4	1426	C	11E	A	170	52.555	29.759	52.086	1.00	11.23	6	47.232	22.145	48.309	1.00	6.73	6
A1H4	1427	C	11E	A	170	51.497	31.920	51.068	1.00	9.11	6	48.624	22.609	47.566	1.00	5.79	6
A1H4	1428	C	11E	A	170	51.497	31.920	51.068	1.00	9.11	6	48.624	22.609	47.566	1.00	5.79	6
A1H4	1429	C	11E	A	170	50.410	32.066	51.383	1.00	8.71	6	50.308	23.922	47.566	1.00	5.00	6
A1H4	1430	C	11E	A	170	52.569	32.897	50.587	1.00	7.13	6	50.308	23.922	47.566	1.00	5.00	6
A1H4	1431	C	11E	A	170	52.569	32.897	50.587	1.00	7.13	6	50.308	23.922	47.566	1.00	5.00	6

1405	CE3 TRP A 182	1538	CA SER A 188	45	109	15	208	41	353	1	00	9	72	6
1406	CE3 TRP A 182	1539	CA SER A 188	46	109	15	208	41	353	1	00	9	72	6
1407	CE3 TRP A 182	1540	CA SER A 188	47	109	15	208	41	353	1	00	9	72	6
1408	CE3 TRP A 182	1541	CA SER A 188	48	109	15	208	41	353	1	00	9	72	6
1409	CE3 TRP A 182	1542	CA SER A 188	49	109	15	208	41	353	1	00	9	72	6
1410	CE3 TRP A 182	1543	CA SER A 188	50	109	15	208	41	353	1	00	9	72	6
1411	CE3 TRP A 182	1544	CA SER A 188	51	110	15	202	46	957	1	00	5	00	6
1412	CE3 TRP A 182	1545	CA SER A 188	52	110	15	202	46	957	1	00	5	00	6
1413	CE3 TRP A 182	1546	CA SER A 188	53	110	15	202	46	957	1	00	5	00	6
1414	CE3 TRP A 182	1547	CA SER A 188	54	110	15	202	46	957	1	00	5	00	6
1415	CE3 TRP A 182	1548	CA SER A 188	55	110	15	202	46	957	1	00	5	00	6
1416	CE3 TRP A 182	1549	CA SER A 188	56	110	15	202	46	957	1	00	5	00	6
1417	CE3 TRP A 182	1550	CA SER A 188	57	110	15	202	46	957	1	00	5	00	6
1418	CE3 TRP A 182	1551	CA SER A 188	58	110	15	202	46	957	1	00	5	00	6
1419	CE3 TRP A 182	1552	CA SER A 188	59	110	15	202	46	957	1	00	5	00	6
1420	CE3 TRP A 182	1553	CA SER A 188	60	110	15	202	46	957	1	00	5	00	6
1421	CE3 TRP A 182	1554	CA SER A 188	61	110	15	202	46	957	1	00	5	00	6
1422	CE3 TRP A 182	1555	CA SER A 188	62	110	15	202	46	957	1	00	5	00	6
1423	CE3 TRP A 182	1556	CA SER A 188	63	110	15	202	46	957	1	00	5	00	6
1424	CE3 TRP A 182	1557	CA SER A 188	64	110	15	202	46	957	1	00	5	00	6
1425	CE3 TRP A 182	1558	CA SER A 188	65	110	15	202	46	957	1	00	5	00	6
1426	CE3 TRP A 182	1559	CA SER A 188	66	110	15	202	46	957	1	00	5	00	6
1427	CE3 TRP A 182	1560	CA SER A 188	67	110	15	202	46	957	1	00	5	00	6
1428	CE3 TRP A 182	1561	CA SER A 188	68	110	15	202	46	957	1	00	5	00	6
1429	CE3 TRP A 182	1562	CA SER A 188	69	110	15	202	46	957	1	00	5	00	6
1430	CE3 TRP A 182	1563	CA SER A 188	70	110	15	202	46	957	1	00	5	00	6
1431	CE3 TRP A 182	1564	CA SER A 188	71	110	15	202	46	957	1	00	5	00	6
1432	CE3 TRP A 182	1565	CA SER A 188	72	110	15	202	46	957	1	00	5	00	6
1433	CE3 TRP A 182	1566	CA SER A 188	73	110	15	202	46	957	1	00	5	00	6
1434	CE3 TRP A 182	1567	CA SER A 188	74	110	15	202	46	957	1	00	5	00	6
1435	CE3 TRP A 182	1568	CA SER A 188	75	110	15	202	46	957	1	00	5	00	6
1436	CE3 TRP A 182	1569	CA SER A 188	76	110	15	202	46	957	1	00	5	00	6
1437	CE3 TRP A 182	1570	CA SER A 188	77	110	15	202	46	957	1	00	5	00	6
1438	CE3 TRP A 182	1571	CA SER A 188	78	110	15	202	46	957	1	00	5	00	6
1439	CE3 TRP A 182	1572	CA SER A 188	79	110	15	202	46	957	1	00	5	00	6
1440	CE3 TRP A 182	1573	CA SER A 188	80	110	15	202	46	957	1	00	5	00	6
1441	CE3 TRP A 182	1574	CA SER A 188	81	110	15	202	46	957	1	00	5	00	6
1442	CE3 TRP A 182	1575	CA SER A 188	82	110	15	202	46	957	1	00	5	00	6
1443	CE3 TRP A 182	1576	CA SER A 188	83	110	15	202	46	957	1	00	5	00	6
1444	CE3 TRP A 182	1577	CA SER A 188	84	110	15	202	46	957	1	00	5	00	6
1445	CE3 TRP A 182	1578	CA SER A 188	85	110	15	202	46	957	1	00	5	00	6
1446	CE3 TRP A 182	1579	CA SER A 188	86	110	15	202	46	957	1	00	5	00	6
1447	CE3 TRP A 182	1580	CA SER A 188	87	110	15	202	46	957	1	00	5	00	6
1448	CE3 TRP A 182	1581	CA SER A 188	88	110	15	202	46	957	1	00	5	00	6
1449	CE3 TRP A 182	1582	CA SER A 188	89	110	15	202	46	957	1	00	5	00	6
1450	CE3 TRP A 182	1583	CA SER A 188	90	110	15	202	46	957	1	00	5	00	6
1451	CE3 TRP A 182	1584	CA SER A 188	91	110	15	202	46	957	1	00	5	00	6
1452	CE3 TRP A 182	1585	CA SER A 188	92	110	15	202	46	957	1	00	5	00	6
1453	CE3 TRP A 182	1586	CA SER A 188	93	110	15	202	46	957	1	00	5	00	6
1454	CE3 TRP A 182	1587	CA SER A 188	94	110	15	202	46	957	1	00	5	00	6
1455	CE3 TRP A 182	1588	CA SER A 188	95	110	15	202	46	957	1	00	5	00	6
1456	CE3 TRP A 182	1589	CA SER A 188	96	110	15	202	46	957	1	00	5	00	6
1457	CE3 TRP A 182	1590	CA SER A 188	97	110	15	202	46	957	1	00	5	00	6
1458	CE3 TRP A 182	1591	CA SER A 188	98	110	15	202	46	957	1	00	5	00	6
1459	CE3 TRP A 182	1592	CA SER A 188	99	110	15	202	46	957	1	00	5	00	6
1460	CE3 TRP A 182	1593	CA SER A 188	100	110	15	202	46	957	1	00	5	00	6

ATOM	1591	O	ASP	A	200	45.308	31.320	47.681	1.00	5.31	8
ATOM	1592	H	VAL	A	201	43.567	31.445	46.359	1.00	5.00	6
ATOM	1593	CA	VAL	A	201	42.610	31.003	47.446	1.00	5.00	6
ATOM	1594	CA	VAL	A	201	41.215	31.999	46.911	1.00	5.00	6
ATOM	1595	CG	VAL	A	201	40.269	32.082	48.070	1.00	5.00	6
ATOM	1596	CG	VAL	A	201	41.205	33.336	46.136	1.00	5.00	6
ATOM	1597	CE1	VAL	A	201	40.616	32.582	47.316	1.00	5.00	6
ATOM	1598	CE2	VAL	A	201	42.305	32.582	47.316	1.00	5.00	6
ATOM	1599	CE2	VAL	A	201	42.605	30.491	47.571	1.00	5.00	7
ATOM	1600	CH	VAL	A	202	42.519	29.430	50.556	1.00	5.00	6
ATOM	1601	CH	VAL	A	202	43.337	29.878	51.401	1.00	5.82	6
ATOM	1602	C	ASP	A	202	43.437	28.934	52.876	1.00	6.39	6
ATOM	1603	C	ASP	A	202	44.017	28.934	52.876	1.00	6.39	6
ATOM	1604	CO	ASP	A	202	44.017	28.934	52.876	1.00	6.39	6
ATOM	1605	C	ASP	A	202	41.060	29.141	50.949	1.00	5.00	6
ATOM	1606	C	ASP	A	202	40.518	29.810	51.838	1.00	5.00	8
ATOM	1607	CO	ASP	A	202	40.418	28.138	50.330	1.00	5.00	7
ATOM	1608	CO	ASP	A	202	39.919	27.925	50.636	1.00	5.09	6
ATOM	1609	CO	ASP	A	202	38.581	28.166	48.426	1.00	5.00	6
ATOM	1610	CO	ASP	A	202	38.008	28.166	48.426	1.00	5.00	6
ATOM	1611	C	ASP	A	203	38.653	28.457	47.236	1.00	5.00	6
ATOM	1612	H	VAL	A	203	38.449	29.510	46.379	1.00	5.00	6
ATOM	1613	CA	VAL	A	203	37.124	29.393	48.827	1.00	5.05	6
ATOM	1614	CA	VAL	A	203	36.914	30.493	47.963	1.00	5.07	6
ATOM	1615	CG	VAL	A	203	37.355	31.406	46.763	1.00	5.11	6
ATOM	1616	CG	VAL	A	203	37.355	31.406	46.763	1.00	5.11	6
ATOM	1617	CE	VAL	A	203	38.899	26.963	51.897	1.00	5.73	6
ATOM	1618	C	ASP	A	203	37.783	26.508	52.205	1.00	5.91	8
ATOM	1619	C	ASP	A	204	39.942	26.807	52.703	1.00	6.06	7
ATOM	1620	H	VAL	A	204	39.883	26.202	54.010	1.00	6.53	6
ATOM	1621	CA	VAL	A	204	41.108	25.454	54.543	1.00	7.71	6
ATOM	1622	CA	VAL	A	204	40.187	24.192	53.738	1.00	9.07	6
ATOM	1623	CG	VAL	A	204	40.287	23.870	53.354	1.00	10.31	8
ATOM	1624	CG	VAL	A	204	42.533	23.870	53.354	1.00	10.31	8
ATOM	1625	CE1	VAL	A	204	39.632	27.395	55.016	1.00	7.25	6
ATOM	1626	CE2	VAL	A	204	39.231	27.113	56.154	1.00	7.19	7
ATOM	1627	CE2	VAL	A	204	39.838	26.671	54.654	1.00	7.01	7
ATOM	1628	CE2	VAL	A	204	40.560	26.773	55.659	1.00	7.00	6
ATOM	1629	CO	VAL	A	204	40.560	26.773	55.659	1.00	7.00	6
ATOM	1630	C	ASP	A	205	40.566	32.025	54.220	1.00	5.15	6
ATOM	1631	C	ASP	A	205	39.590	32.373	55.780	1.00	5.16	6
ATOM	1632	CH	VAL	A	205	41.751	32.331	56.910	1.00	8.31	7
ATOM	1633	CH	VAL	A	205	41.525	33.260	57.828	1.00	6.29	6
ATOM	1634	CE1	VAL	A	205	40.214	33.513	57.752	1.00	8.24	7
ATOM	1635	CE2	VAL	A	205	37.511	30.307	52.825	1.00	7.75	8
ATOM	1636	C	ASP	A	205	37.511	30.307	52.825	1.00	7.75	8
ATOM	1637	C	ASP	A	206	37.511	29.968	56.988	1.00	6.98	7
ATOM	1638	CA	VAL	A	206	38.242	29.637	58.262	1.00	6.83	6
ATOM	1639	CA	VAL	A	206	36.134	30.164	57.160	1.00	6.77	6
ATOM	1640	CG	VAL	A	206	35.778	29.837	58.641	1.00	6.82	6
ATOM	1641	CG	VAL	A	206	35.778	29.837	58.641	1.00	6.82	6
ATOM	1642	CO	ASP	A	200	35.653	31.519	57.263	1.00	6.98	6
ATOM	1643	C	ASP	A	206	34.527	31.408	56.238	1.00	6.33	8





AIOM	1909	N	ALA	A	233	37,399	25,223	37,416	1,00	5,45	7
AIOM	1910	CA	ALA	A	233	36,848	24,620	38,465	1,00	5,45	6
AIOM	1911	CB	ALA	A	233	35,529	23,866	37,899	1,00	6,05	6
AIOM	1912	C	ALA	A	233	37,755	23,310	38,952	1,00	6,00	6
AIOM	1913	C	ALA	A	233	37,565	22,963	40,144	1,00	6,61	8
AIOM	1914	CA	LFS	A	234	38,688	22,764	38,169	1,00	5,81	7
AIOM	1915	CA	LFS	A	234	38,688	22,764	38,169	1,00	5,81	7
AIOM	1916	CB	LFS	A	234	40,171	20,929	37,405	1,00	5,76	6
AIOM	1917	CB	LFS	A	234	41,275	21,620	36,704	1,00	6,41	6
AIOM	1918	CB	LFS	A	234	41,863	20,613	35,971	1,00	7,10	6
AIOM	1919	CB	LFS	A	234	43,118	21,208	34,994	1,00	5,42	6
AIOM	1920	HZ	LFS	A	234	43,541	20,287	33,901	1,00	5,00	7
AIOM	1921	HZ	LFS	A	234	43,541	20,287	33,901	1,00	5,00	7
AIOM	1922	C	LFS	A	234	44,110	21,286	33,343	1,00	5,57	6
AIOM	1923	C	LFS	A	234	44,110	21,286	33,343	1,00	5,57	6
AIOM	1924	CA	HIS	A	235	40,709	23,488	39,791	1,00	6,73	7
AIOM	1925	CA	HIS	A	235	41,640	23,999	40,796	1,00	6,75	6
AIOM	1926	CB	HIS	A	235	42,097	25,195	40,296	1,00	6,58	6
AIOM	1927	CB	HIS	A	235	43,030	24,789	38,959	1,00	6,14	6
AIOM	1928	CB	HIS	A	235	42,735	25,085	37,784	1,00	7,29	6
AIOM	1929	CB	HIS	A	235	44,290	23,755	37,502	1,00	7,1	6
AIOM	1930	ME2	HIS	A	235	43,386	24,446	36,829	1,00	6,22	7
AIOM	1931	C	HIS	A	235	40,857	26,459	42,002	1,00	6,76	6
AIOM	1932	C	HIS	A	235	41,512	25,042	42,814	1,00	6,54	8
AIOM	1933	H	ILE	A	236	39,383	25,341	42,255	1,00	6,68	7
AIOM	1934	H	ILE	A	236	39,383	25,341	42,255	1,00	6,68	7
AIOM	1935	CB	ILE	A	236	37,059	25,946	43,023	1,00	5,90	6
AIOM	1936	CB	ILE	A	236	37,089	26,450	44,213	1,00	6,00	6
AIOM	1937	CB	ILE	A	236	38,558	27,103	44,238	1,00	5,00	6
AIOM	1938	CB	ILE	A	236	38,581	27,999	44,145	1,00	5,00	6
AIOM	1939	C	ILE	A	236	38,228	23,724	44,193	1,00	7,20	6
AIOM	1940	C	ILE	A	236	37,397	22,652	43,555	1,00	7,08	6
AIOM	1941	C	ILE	A	236	37,397	22,652	43,555	1,00	7,08	6
AIOM	1942	CA	LFS	A	237	37,371	22,683	44,264	1,00	7,74	6
AIOM	1943	CB	LFS	A	237	37,428	23,688	44,424	1,00	9,45	6
AIOM	1944	CB	LFS	A	237	37,428	23,688	44,424	1,00	9,45	6
AIOM	1945	CB	LFS	A	237	37,355	22,243	43,831	1,00	12,16	6
AIOM	1946	CB	LFS	A	237	37,357	22,643	43,263	1,00	15,99	6
AIOM	1947	CB	LFS	A	237	37,992	23,114	51,189	1,00	19,56	6
AIOM	1948	CB	LFS	A	237	37,279	22,767	52,623	1,00	22,41	7
AIOM	1949	D	LFS	A	237	37,279	22,767	52,623	1,00	22,41	7
AIOM	1950	D	LFS	A	237	38,561	23,187	45,459	1,00	7,55	6
AIOM	1951	N	PHE	A	238	36,210	21,062	45,551	1,00	7,27	6
AIOM	1951	CA	PHE	A	238	34,912	20,689	44,944	1,00	8,77	6
AIOM	1952	CB	PHE	A	238	34,921	19,232	44,425	1,00	8,77	6
AIOM	1953	CB	PHE	A	238	35,992	18,884	43,442	1,00	9,75	6
AIOM	1954	CB	PHE	A	238	35,992	18,884	43,442	1,00	9,75	6
AIOM	1955	CB2	PHE	A	238	36,959	17,529	45,199	1,00	9,45	6
AIOM	1956	CE1	PHE	A	238	37,658	19,448	41,787	1,00	9,12	6
AIOM	1957	CE2	PHE	A	238	37,220	17,125	42,292	1,00	8,63	6
AIOM	1958	CB	PHE	A	238	37,882	18,097	41,562	1,00	9,31	6
AIOM	1959	C	PHE	A	238	33,694	20,870	45,841	1,00	7,47	6
AIOM	1960	N	SR	A	239	32,666	21,356	45,350	1,00	7,57	6
AIOM	1961	N	SR	A	239	33,081	20,475	47,113	1,00	7,50	7

## SUBSTITUTE SHEET (RULE 26)

28.727	31.959	42.086	1.00	10.45	6	ATON	2068	CA	ALA A 251	19.029	33.079	48.862	1.00	16.06	6
28.762	31.959	42.086	1.00	9.28	6	ATON	2069	CB	ALA A 251	19.271	33.749	49.765	1.00	16.27	6
28.797	31.959	42.086	1.00	8.11	6	ATON	2070	C	ALA A 251	18.376	33.749	49.765	1.00	16.27	6
26.051	29.168	44.164	1.00	8.82	8	ATON	2071	M	THR A 252	17.596	34.738	48.088	1.00	16.47	8
27.217	27.284	45.056	1.00	9.46	7	ATON	2072	M	THR A 252	18.343	33.433	46.476	1.00	16.21	7
26.082	27.305	44.114	1.00	10.52	6	ATON	2073	CA	THR A 252	17.463	34.224	45.487	1.00	16.03	6
26.186	26.185	43.039	1.00	12.05	6	ATON	2074	CA	THR A 252	18.462	34.328	44.189	1.00	13.96	6
24.932	26.185	43.039	1.00	13.35	6	ATON	2075	CE1	THR A 252	18.977	32.968	43.324	1.00	11.77	6
24.932	26.185	43.039	1.00	13.35	6	ATON	2076	CE2	THR A 252	18.977	32.968	43.324	1.00	11.77	6
24.722	27.203	44.853	1.00	10.43	6	ATON	2077	C	THR A 252	16.292	33.577	45.170	1.00	16.40	6
23.758	27.906	44.590	1.00	10.02	8	ATON	2078	G	THR A 252	15.441	34.281	44.629	1.00	16.40	8
24.745	26.269	45.790	1.00	11.30	7	ATON	2079	G	THR A 252	16.139	32.267	45.429	1.00	16.68	7
23.552	26.072	46.634	1.00	12.37	6	ATON	2080	CA	GLT A 253	14.955	31.502	45.148	1.00	16.75	6
23.552	26.072	46.634	1.00	12.37	6	ATON	2081	CA	GLT A 253	14.955	31.502	45.148	1.00	16.75	6
23.552	26.072	46.634	1.00	12.37	6	ATON	2082	C	GLT A 253	13.985	30.402	43.957	1.00	17.06	6
23.552	26.072	46.634	1.00	12.37	6	ATON	2083	CA	LVS A 254	16.018	31.475	42.888	1.00	17.07	7
23.367	23.366	49.350	1.00	37.61	8	ATON	2084	CA	LVS A 254	16.045	31.196	41.437	1.00	16.76	6
25.476	22.642	49.028	1.00	36.61	7	ATON	2085	CB	LVS A 254	16.734	32.377	40.748	1.00	18.37	6
23.153	27.225	47.485	1.00	12.39	6	ATON	2086	CB	LVS A 254	16.007	33.685	40.568	1.00	21.23	6
21.970	27.261	44.590	1.00	12.24	9	ATON	2087	CD	LVS A 254	16.344	34.084	40.336	1.00	23.96	6
21.970	27.261	44.590	1.00	12.24	9	ATON	2088	CD	LVS A 254	16.344	34.084	40.336	1.00	23.96	6
23.852	29.144	44.803	1.00	12.41	6	ATON	2089	WZ	LVS A 254	10.349	36.723	39.792	1.00	27.00	7
25.094	29.791	49.517	1.00	12.47	6	ATON	2090	C	LVS A 254	16.731	29.871	41.097	1.00	16.34	6
23.231	30.263	48.050	1.00	12.74	6	ATON	2091	O	LVS A 254	17.533	29.323	41.896	1.00	16.45	8
22.308	30.857	48.561	1.00	12.85	8	ATON	2092	M	GLU A 255	16.459	29.313	39.928	1.00	15.71	7
23.150	31.495	48.938	1.00	12.79	7	ATON	2093	CA	GLU A 255	17.084	28.072	39.466	1.00	15.30	6
23.150	31.495	48.938	1.00	12.79	7	ATON	2094	CA	GLU A 255	16.954	26.337	38.102	1.00	16.71	6
24.009	31.680	44.684	1.00	11.87	6	ATON	2095	CG	GLU A 255	16.954	26.337	38.102	1.00	16.71	6
23.357	32.721	43.754	1.00	12.19	6	ATON	2096	CD	GLU A 255	16.927	26.270	36.420	1.00	29.50	6
25.400	32.171	45.014	1.00	11.42	6	ATON	2097	CE1	GLU A 255	17.033	26.945	35.393	1.00	31.45	8
21.748	31.040	45.537	1.00	12.91	6	ATON	2098	DE2	GLU A 255	17.730	25.553	35.340	1.00	31.98	8
20.866	30.989	45.505	1.00	12.81	9	ATON	2099	C	GLU A 255	18.623	28.183	39.365	1.00	14.27	6
20.866	30.989	45.505	1.00	12.81	9	ATON	2100	O	GLU A 255	19.417	27.324	39.733	1.00	14.14	8
20.124	29.352	44.897	1.00	13.92	6	ATON	2101	C	GLU A 255	20.476	29.643	38.459	1.00	13.25	7
20.066	27.906	44.404	1.00	11.75	6	ATON	2102	CA	HE1 A 256	20.476	29.643	38.459	1.00	13.25	7
20.681	27.726	43.033	1.00	11.59	6	ATON	2103	CB	HE1 A 256	21.171	29.970	39.998	1.00	12.38	6
20.814	26.274	42.576	1.00	12.59	6	ATON	2104	CD	HE1 A 256	20.740	31.237	40.705	1.00	13.41	6
21.411	26.198	41.724	1.00	13.02	7	ATON	2105	CG	HE1 A 256	20.539	32.774	39.751	1.00	13.00	16
21.411	26.198	41.724	1.00	13.02	7	ATON	2106	CE	HE1 A 256	22.245	33.221	39.432	1.00	12.60	6
22.150	24.051	41.426	1.00	11.64	7	ATON	2107	C	HE1 A 256	21.209	29.486	37.966	1.00	11.87	6
22.589	25.166	39.515	1.00	15.22	7	ATON	2108	C	HE1 A 256	20.904	28.261	36.805	1.00	11.99	9
19.215	29.503	46.125	1.00	14.55	6	ATON	2109	H	PHE A 257	20.802	28.261	35.918	1.00	10.24	6
18.082	30.005	45.970	1.00	14.34	8	ATON	2110	CA	PHE A 257	21.412	27.347	34.397	1.00	9.31	6
19.685	29.166	47.359	1.00	15.16	7	ATON	2111	CB	PHE A 257	22.056	26.339	33.591	1.00	9.08	6
19.685	29.166	47.359	1.00	15.16	7	ATON	2112	CB	PHE A 257	21.434	25.032	33.491	1.00	7.86	6
19.437	28.816	49.790	1.00	15.15	6	ATON	2113	CE1	PHE A 257	22.428	24.132	32.769	1.00	8.44	6
18.902	27.546	50.440	1.00	28.24	6	ATON	2114	CE2	PHE A 257	22.428	24.132	32.769	1.00	8.44	6
20.067	26.619	50.807	1.00	32.12	6	ATON	2115	CE3	PHE A 257	22.428	24.132	32.769	1.00	8.44	6
21.116	27.047	51.333	1.00	34.30	8	ATON	2116	CE4	PHE A 257	24.059	25.461	32.927	1.00	9.08	6
19.707	25.331	48.719	1.00	32.80	7	ATON	2117	CE5	PHE A 257	23.624	26.537	32.171	1.00	10.03	6
19.707	25.331	48.719	1.00	32.80	7	ATON	2118	C	PHE A 257	23.155	28.593	35.647	1.00	9.70	6
17.196	31.022	48.071	1.00	15.85	9	ATON	2119	C	PHE A 257	23.155	28.593	35.647	1.00	9.70	6
19.316	31.621	48.691	1.00	15.85	7	ATON	2120	H	THR A 258	23.933	28.447	36.329	1.00	9.20	8

10M	25.392	26.409	36.550	1.00	6	ATOM	2175	CA	GLU A 264	39.758	18.950	31.301	1.00	10.57	6	ATOM	2175	CA	GLU A 264	
10M	25.824	26.583	37.938	1.00	6	ATOM	2176	CA	GLU A 264	40.441	17.607	31.185	1.00	10.92	6	ATOM	2176	CA	GLU A 264	
10M	27.337	27.678	38.117	1.00	7.38	6	ATOM	2177	CA	GLU A 264	40.619	16.999	32.536	1.00	14.66	6	ATOM	2177	CA	GLU A 264
10M	27.337	28.720	38.142	1.00	8.42	6	ATOM	2178	CA	GLU A 264	41.796	16.043	32.600	1.00	18.65	6	ATOM	2178	CA	GLU A 264
10M	25.766	25.533	35.666	1.00	8.29	6	ATOM	2179	CA	GLU A 264	41.972	15.344	33.934	1.00	20.60	6	ATOM	2179	CA	GLU A 264
10M	25.766	24.341	35.666	1.00	9.22	8	ATOM	2180	CA	GLU A 264	41.214	15.481	34.907	1.00	24.23	8	ATOM	2180	CA	GLU A 264
10M	27.160	25.972	34.922	1.00	7.82	7	ATOM	2181	CA	GLU A 264	42.996	14.478	34.067	1.00	23.90	7	ATOM	2181	CA	GLU A 264
10M	27.160	25.972	34.922	1.00	7.82	7	ATOM	2182	CA	GLU A 264	42.996	14.478	34.067	1.00	23.90	7	ATOM	2182	CA	GLU A 264
10M	27.859	25.175	35.564	1.00	5.00	6	ATOM	2183	CA	GLU A 264	38.641	16.411	30.232	1.00	11.01	6	ATOM	2183	CA	GLU A 264
10M	28.101	26.589	32.036	1.00	5.00	6	ATOM	2184	CA	GLU A 264	40.454	16.216	29.289	1.00	11.25	6	ATOM	2184	CA	GLU A 264
10M	28.799	24.202	31.809	1.00	5.00	6	ATOM	2185	CA	GLU A 264	40.151	15.322	28.269	1.00	11.87	6	ATOM	2185	CA	GLU A 264
10M	29.428	25.381	34.552	1.00	7.58	6	ATOM	2186	CA	GLU A 264	41.223	15.365	27.078	1.00	11.52	6	ATOM	2186	CA	GLU A 264
10M	29.428	24.352	34.634	1.00	7.58	6	ATOM	2187	CA	GLU A 264	40.655	14.637	25.854	1.00	12.03	6	ATOM	2187	CA	GLU A 264
10M	31.555	24.487	35.344	1.00	6.08	6	ATOM	2188	CA	GLU A 264	41.465	14.762	25.854	1.00	11.46	6	ATOM	2188	CA	GLU A 264
10M	31.555	24.487	35.344	1.00	6.08	6	ATOM	2189	CA	GLU A 264	41.465	14.762	25.854	1.00	11.46	6	ATOM	2189	CA	GLU A 264
10M	31.942	23.621	36.516	1.00	7.64	6	ATOM	2190	CA	GLU A 264	40.028	13.873	28.691	1.00	12.36	6	ATOM	2190	CA	GLU A 264
10M	32.523	25.076	34.215	1.00	8.28	6	ATOM	2191	CA	GLU A 264	40.755	13.007	28.282	1.00	12.25	6	ATOM	2191	CA	GLU A 264
10M	32.523	24.991	33.536	1.00	8.28	6	ATOM	2192	CA	GLU A 264	39.116	13.676	29.634	1.00	13.06	7	ATOM	2192	CA	GLU A 264
10M	31.579	24.848	34.097	1.00	8.43	6	ATOM	2193	CA	GLU A 264	38.844	12.428	30.337	1.00	13.75	6	ATOM	2193	CA	GLU A 264
10M	31.579	24.848	34.097	1.00	8.43	6	ATOM	2194	CA	GLU A 264	38.844	12.428	30.337	1.00	13.75	6	ATOM	2194	CA	GLU A 264
10M	35.342	25.828	32.036	1.00	5.00	6	ATOM	2195	CA	GLU A 264	40.150	16.216	29.289	1.00	11.52	6	ATOM	2195	CA	GLU A 264
10M	35.342	25.828	32.036	1.00	5.00	6	ATOM	2196	CA	GLU A 264	40.150	16.216	29.289	1.00	11.52	6	ATOM	2196	CA	GLU A 264
10M	36.281	25.350	31.518	1.00	13.13	6	ATOM	2197	CA	GLU A 264	41.311	10.519	31.969	1.00	22.43	7	ATOM	2197	CA	GLU A 264
10M	36.823	26.339	30.525	1.00	23.18	6	ATOM	2198	CA	GLU A 264	35.100	10.410	32.662	1.00	20.13	7	ATOM	2198	CA	GLU A 264
10M	36.068	26.970	29.694	1.00	25.81	8	ATOM	2199	CA	GLU A 264	37.441	12.394	30.944	1.00	13.73	6	ATOM	2199	CA	GLU A 264
10M	38.008	26.441	30.593	1.00	25.35	8	ATOM	2200	CA	GLU A 264	37.161	12.331	31.927	1.00	13.68	8	ATOM	2200	CA	GLU A 264
10M	35.644	23.659	33.817	1.00	8.48	6	ATOM	2201	CA	GLU A 264	36.552	11.545	30.362	1.00	13.47	7	ATOM	2201	CA	GLU A 264
10M	35.644	23.659	33.817	1.00	8.48	6	ATOM	2202	CA	GLU A 264	36.552	11.545	30.362	1.00	13.47	7	ATOM	2202	CA	GLU A 264
10M	35.678	22.739	32.733	1.00	8.57	6	ATOM	2203	CA	GLU A 264	34.195	11.554	32.027	1.00	13.44	6	ATOM	2203	CA	GLU A 264
10M	36.500	21.387	34.293	1.00	8.87	6	ATOM	2204	CA	GLU A 264	34.195	11.554	32.027	1.00	13.44	6	ATOM	2204	CA	GLU A 264
10M	35.838	20.183	34.966	1.00	8.94	6	ATOM	2205	CA	GLU A 264	35.918	10.566	32.733	1.00	12.97	7	ATOM	2205	CA	GLU A 264
10M	36.761	19.321	35.821	1.00	9.11	6	ATOM	2206	CA	GLU A 264	35.918	10.566	32.733	1.00	12.97	7	ATOM	2206	CA	GLU A 264
10M	36.660	19.322	37.206	1.00	9.01	6	ATOM	2207	CA	GLU A 264	36.184	10.653	35.146	1.00	13.05	6	ATOM	2207	CA	GLU A 264
10M	37.509	18.176	37.984	1.00	9.15	6	ATOM	2208	CA	GLU A 264	35.512	10.656	36.213	1.00	13.01	8	ATOM	2208	CA	GLU A 264
10M	38.405	17.233	36.023	1.00	9.45	6	ATOM	2209	CA	GLU A 264	37.125	11.575	34.879	1.00	12.90	7	ATOM	2209	CA	GLU A 264
10M	38.405	17.233	36.023	1.00	9.45	6	ATOM	2210	CA	GLU A 264	37.125	11.575	34.879	1.00	12.90	7	ATOM	2210	CA	GLU A 264
10M	38.490	17.788	37.415	1.00	9.42	6	ATOM	2211	CA	GLU A 264	38.700	13.294	35.149	1.00	12.04	6	ATOM	2211	CA	GLU A 264
10M	39.305	17.012	38.214	1.00	9.41	6	ATOM	2212	CA	GLU A 264	39.840	12.506	36.217	1.00	22.75	6	ATOM	2212	CA	GLU A 264
10M	37.424	20.777	33.104	1.00	8.97	6	ATOM	2213	CA	GLU A 264	40.869	12.034	35.211	1.00	27.74	6	ATOM	2213	CA	GLU A 264
10M	37.008	20.107	32.297	1.00	9.09	6	ATOM	2214	CA	GLU A 264	41.722	10.885	35.785	1.00	30.85	6	ATOM	2214	CA	GLU A 264
10M	39.403	21.382	32.155	1.00	9.15	6	ATOM	2215	CA	GLU A 264	42.663	10.564	34.698	1.00	32.23	7	ATOM	2215	CA	GLU A 264
10M	39.403	21.382	32.155	1.00	9.15	6	ATOM	2216	CA	GLU A 264	42.663	10.564	34.698	1.00	32.23	7	ATOM	2216	CA	GLU A 264
10M	40.183	22.560	31.346	1.00	9.45	6	ATOM	2217	CA	GLU A 264	35.698	13.909	34.556	1.00	12.65	6	ATOM	2217	CA	GLU A 264
10M	40.638	22.366	29.917	1.00	11.66	6	ATOM	2218	CA	GLU A 264	34.539	14.810	34.538	1.00	12.16	6	ATOM	2218	CA	GLU A 264
10M	39.892	22.703	28.733	1.00	12.75	6	ATOM	2219	CA	GLU A 264	34.184	15.161	33.088	1.00	13.49	6	ATOM	2219	CA	GLU A 264
10M	40.662	22.299	27.612	1.00	13.78	6	ATOM	2220	CA	GLU A 264	34.959	16.348	32.467	1.00	13.12	6	ATOM	2220	CA	GLU A 264
10M	38.631	23.289	28.512	1.00	12.04	6	ATOM	2221	CA	GLU A 264	34.614	17.623	33.197	1.00	13.62	6	ATOM	2221	CA	GLU A 264
10M	40.213	21.333	29.507	1.00	12.57	6	ATOM	2222	CA	GLU A 264	35.145	16.210	32.550	1.00	11.76	6	ATOM	2222	CA	GLU A 264
10M	41.820	21.733	28.299	1.00	10.77	6	ATOM	2223	CA	GLU A 264	32.700	14.465	32.700	1.00	13.45	6	ATOM	2223	CA	GLU A 264
10M	40.205	22.513	26.299	1.00	16.12	6	ATOM	2224	CA	GLU A 264	32.700	14.465	32.700	1.00	13.45	6	ATOM	2224	CA	GLU A 264
10M	38.291	23.453	27.210	1.00	10.88	6	ATOM	2225	CA	GLU A 264	32.700	14.465	32.700	1.00	13.45	6	ATOM	2225	CA	GLU A 264
10M	38.970	23.084	26.122	1.00	11.77	6	ATOM	2226	CA	GLU A 264	32.700	14.465	32.700	1.00	13.45	6	ATOM	2226	CA	GLU A 264
10M	40.303	20.953	31.833	1.00	10.24	6	ATOM	2227	CA	GLU A 264	32.136	12.851	35.281	1.00	11.41	7	ATOM	2227	CA	GLU A 264
10M	41.436	20.018	32.294	1.00	10.24	8	ATOM	2228	CA	GLU A 264	32.136	12.851	35.281	1.00	11.41	7	ATOM	2228	CA	GLU A 264

**SUBSTITUTE SHEET (RULE 26)**

29.173	18.187	43.406	1.00	12.78	6
29.220	19.264	42.357	1.00	12.02	6
29.267	20.341	41.308	1.00	11.26	6
29.314	21.418	40.259	1.00	10.50	6
29.361	22.495	39.210	1.00	9.74	6
29.408	23.572	38.161	1.00	8.98	6
29.455	24.649	37.112	1.00	8.22	6
29.502	25.726	36.063	1.00	7.46	6
29.549	26.803	35.014	1.00	6.70	6
29.596	27.880	33.965	1.00	5.94	6
29.643	28.957	32.916	1.00	5.18	6
29.690	30.034	31.867	1.00	4.42	6
29.737	31.111	30.818	1.00	3.66	6
29.784	32.188	29.769	1.00	2.90	6
29.831	33.265	28.720	1.00	2.14	6
29.878	34.342	27.671	1.00	1.38	6
29.925	35.419	26.622	1.00	0.62	6
29.972	36.496	25.573	1.00	-0.14	6
30.019	37.573	24.524	1.00	-0.90	6
30.066	38.650	23.475	1.00	-1.66	6
30.113	39.727	22.426	1.00	-2.42	6
30.160	40.804	21.377	1.00	-3.18	6
30.207	41.881	20.328	1.00	-3.94	6
30.254	42.958	19.279	1.00	-4.70	6
30.301	44.035	18.230	1.00	-5.46	6
30.348	45.112	17.181	1.00	-6.22	6
30.395	46.189	16.132	1.00	-6.98	6
30.442	47.266	15.083	1.00	-7.74	6
30.489	48.343	14.034	1.00	-8.50	6
30.536	49.420	12.985	1.00	-9.26	6
30.583	50.497	11.936	1.00	-10.02	6
30.630	51.574	10.887	1.00	-10.78	6
30.677	52.651	9.838	1.00	-11.54	6
30.724	53.728	8.789	1.00	-12.30	6
30.771	54.805	7.740	1.00	-13.06	6
30.818	55.882	6.691	1.00	-13.82	6
30.865	56.959	5.642	1.00	-14.58	6
30.912	58.036	4.593	1.00	-15.34	6
30.959	59.113	3.544	1.00	-16.10	6
31.006	60.190	2.495	1.00	-16.86	6
31.053	61.267	1.446	1.00	-17.62	6
31.100	62.344	0.397	1.00	-18.38	6
31.147	63.421	-0.652	1.00	-19.14	6
31.194	64.498	-1.703	1.00	-19.90	6
31.241	65.575	-2.754	1.00	-20.66	6
31.288	66.652	-3.805	1.00	-21.42	6
31.335	67.729	-4.856	1.00	-22.18	6
31.382	68.806	-5.907	1.00	-22.94	6
31.429	69.883	-6.958	1.00	-23.70	6
31.476	70.960	-8.009	1.00	-24.46	6
31.523	72.037	-9.060	1.00	-25.22	6
31.570	73.114	-10.111	1.00	-25.98	6
31.617	74.191	-11.162	1.00	-26.74	6
31.664	75.268	-12.213	1.00	-27.50	6
31.711	76.345	-13.264	1.00	-28.26	6
31.758	77.422	-14.315	1.00	-29.02	6
31.805	78.499	-15.366	1.00	-29.78	6
31.852	79.576	-16.417	1.00	-30.54	6
31.899	80.653	-17.468	1.00	-31.30	6
31.946	81.730	-18.519	1.00	-32.06	6
31.993	82.807	-19.570	1.00	-32.82	6
32.040	83.884	-20.621	1.00	-33.58	6
32.087	84.961	-21.672	1.00	-34.34	6
32.134	86.038	-22.723	1.00	-35.10	6
32.181	87.115	-23.774	1.00	-35.86	6
32.228	88.192	-24.825	1.00	-36.62	6
32.275	89.269	-25.876	1.00	-37.38	6
32.322	90.346	-26.927	1.00	-38.14	6
32.369	91.423	-27.978	1.00	-38.90	6
32.416	92.500	-29.029	1.00	-39.66	6
32.463	93.577	-30.080	1.00	-40.42	6
32.510	94.654	-31.131	1.00	-41.18	6
32.557	95.731	-32.182	1.00	-41.94	6
32.604	96.808	-33.233	1.00	-42.70	6
32.651	97.885	-34.284	1.00	-43.46	6
32.698	98.962	-35.335	1.00	-44.22	6
32.745	100.039	-36.386	1.00	-44.98	6
32.792	101.116	-37.437	1.00	-45.74	6
32.839	102.193	-38.488	1.00	-46.50	6
32.886	103.270	-39.539	1.00	-47.26	6
32.933	104.347	-40.590	1.00	-48.02	6
32.980	105.424	-41.641	1.00	-48.78	6
33.027	106.501	-42.692	1.00	-49.54	6
33.074	107.578	-43.743	1.00	-50.30	6
33.121	108.655	-44.794	1.00	-51.06	6
33.168	109.732	-45.845	1.00	-51.82	6
33.215	110.809	-46.896	1.00	-52.58	6
33.262	111.886	-47.947	1.00	-53.34	6
33.309	112.963	-48.998	1.00	-54.10	6
33.356	114.040	-50.049	1.00	-54.86	6
33.403	115.117	-51.100	1.00	-55.62	6
33.450	116.194	-52.151	1.00	-56.38	6
33.497	117.271	-53.202	1.00	-57.14	6
33.544	118.348	-54.253	1.00	-57.90	6
33.591	119.425	-55.304	1.00	-58.66	6
33.638	120.502	-56.355	1.00	-59.42	6
33.685	121.579	-57.406	1.00	-60.18	6
33.732	122.656	-58.457	1.00	-60.94	6
33.779	123.733	-59.508	1.00	-61.70	6
33.826	124.810	-60.559	1.00	-62.46	6
33.873	125.887	-61.610	1.00	-63.22	6
33.920	126.964	-62.661	1.00	-63.98	6
33.967	128.041	-63.712	1.00	-64.74	6
34.014	129.118	-64.763	1.00	-65.50	6
34.061	130.195	-65.814	1.00	-66.26	6
34.108	131.272	-66.865	1.00	-67.02	6
34.155	132.349	-67.916	1.00	-67.78	6
34.202	133.426	-68.967	1.00	-68.54	6
34.249	134.503	-70.018	1.00	-69.30	6
34.296	135.580	-71.069	1.00	-70.06	6
34.343	136.657	-72.120	1.00	-70.82	6
34.390	137.734	-73.171	1.00	-71.58	6
34.437	138.811	-74.222	1.00	-72.34	6
34.484	139.888	-75.273	1.00	-73.10	6
34.531	140.965	-76.324	1.00	-73.86	6
34.578	142.042	-77.375	1.00	-74.62	6
34.625	143.119	-78.426	1.00	-75.38	6
34.672	144.196	-79.477	1.00	-76.14	6
34.719	145.273	-80.528	1.00	-76.90	6
34.766	146.350	-81.579	1.00	-77.66	6
34.813	147.427	-82.630	1.00	-78.42	6
34.860	148.504	-83.681	1.00	-79.18	6
34.907	149.581	-84.732	1.00	-79.94	6
34.954	150.658	-85.783	1.00	-80.70	6
35.001	151.735	-86.834	1.00	-81.46	6
35.048	152.812	-87.885	1.00	-82.22	6
35.095	153.889	-88.936	1.00	-82.98	6
35.142	154.966	-90.000	1.00	-83.74	6
35.189	156.043	-91.051	1.00	-84.50	6
35.236	157.120	-92.102	1.00	-85.26	6
35.283	158.197	-93.153	1.00	-86.02	6
35.330	159.274	-94.204	1.00	-86.78	6
35.377	160.351	-95.255	1.00	-87.54	6
35.424	161.428	-96.306	1.00	-88.30	6
35.471	162.505	-97.357	1.00	-89.06	6
35.518	163.582	-98.408	1.00	-89.82	6
35.565	164.659	-99.459	1.00	-90.58	6
35.612	165.736	-100.510	1.00	-91.34	6
35.659	166.813	-101.561	1.00	-92.10	6
35.706	167.890	-102.612	1.00	-92.86	6
35.753	168.967	-103.663	1.00	-93.62	6
35.800	170.044	-104.714	1.00	-94.38	6
35.847	171.121	-105.765	1.00	-95.14	6
35.894	172.198	-106.816	1.00	-95.90	6
35.941	173.275	-107.867	1.00	-96.66	6
35.988	174.352	-108.918	1.00	-97.42	6
36.035	175.429	-109.969	1.00	-98.18	6
36.082	176.506	-111.020	1.00	-98.94	6
36.129	177.583	-112.071	1.00	-99.70	6
36.176	178.660	-113.122	1.00	-100.46	6
36.223	179.737	-114.173	1.00	-101.22	6
36.270	180.814	-115.224	1.00	-101.98	6
36.317	181.891	-116.275	1.00	-102.74	6
36.364	182.968	-117.326	1.00	-103.50	6
36.411	184.045	-118.377	1.00	-104.26	6
36.458	185.122	-119.428	1.00	-105.02	6
36.505	186.199	-120.479	1.00	-105.78	6
36.552	187.276	-121.530	1.00	-106.54	6
36.599	188.353	-122.581	1.00	-107.30	6
36.646	189.430	-123.632	1.00	-108.06	6
36.693	190.507	-124.683	1.00	-108.82	6
36.740	191.584	-125.734	1.00	-109.58	6
36.787	192.661	-126.785	1.00	-110.34	6
36.834	193.738	-127.836	1.00	-111.10	6
36.881	194.815	-128.887	1.00	-111.86	6
36.928	195.892	-129.938	1.00	-112.62	6
36.975	196.969	-130.989	1.00	-113.38	6
37.022	198.046	-132.040	1.00	-114.14	6
37.069	199.123	-133.091	1.00	-114.90	6
37.116	200.200	-134.142	1.00	-115.66	6
37.163	201.277	-135.193	1.00	-116.42	6
37.210	202.354	-136.244	1.00	-117.18	6
37.257	203.431	-137.295	1.00	-117.94	6
37.304	204.508	-138.346	1.00	-118.70	6
37.351	205.585	-139.397	1.00	-119.46	6
37.398	206.662	-140.448	1.00	-120.22	6
37.445	207.739	-141.499	1.00	-120.98	6
37.492	208.816	-142.550	1.00	-121.74	6
37.539	209.893	-143.601	1.00	-122.50	6
37.586	210.970	-144.652	1.00	-123.26	6
37.633	212.047	-145.703	1.00	-124.02	6
37.680	213.124	-146.754	1.00	-124.78	6
37.727	214.201	-147.805	1.00	-125.54	6
37.774	215.278	-148.856	1.00	-126.30	6
37.821	216.355	-149.907	1.00	-127.06	6
37.868	217.432	-150.958	1.00	-127.82	6
37.915	218.509	-152.009	1.00	-128.58	6
37.962	219.586	-153.060	1.00	-129.34	6
38.009	220.663	-154.111	1.00	-130.10	6
38.056	221.740	-155.162	1.00	-130.86	6
38.103	222.817	-156.213	1.00	-131.62	6
38.150	223.894	-157.264	1		

1014	2133	N	PHE A 284	31.212	21.483	30.801	1.00	7.72	7
1015	2134	CA	PHE A 284	31.460	21.509	30.183	1.00	7.64	6
1016	2135	CG	PHE A 284	31.460	21.509	30.183	1.00	7.64	6
1017	2136	CG	PHE A 284	31.951	24.040	29.240	1.00	7.61	6
1018	2137	CG	PHE A 284	32.301	24.866	30.277	1.00	7.60	6
1019	2138	CG	PHE A 284	31.062	24.475	28.352	1.00	7.80	6
1020	2139	CG	PHE A 284	31.782	26.167	30.312	1.00	8.33	6
1021	2140	CE	PHE A 284	30.501	25.756	28.282	1.00	6.48	6
1022	2141	CE	PHE A 284	30.501	25.756	28.282	1.00	6.48	6
1023	2142	CE	PHE A 284	31.892	26.212	28.924	1.00	7.66	6
1024	2143	CG	PHE A 284	32.633	19.958	29.627	1.00	7.52	8
1025	2144	H	PHE A 285	31.517	19.574	29.741	1.00	7.99	7
1026	2145	CA	ASP A 285	31.997	18.452	27.212	1.00	8.11	6
1027	2146	CA	ASP A 285	30.919	17.867	26.269	1.00	8.64	6
1028	2147	CG	ASP A 285	31.997	18.452	27.212	1.00	8.11	6
1029	2148	CG	ASP A 285	31.973	15.771	26.269	1.00	8.07	6
1030	2149	CG	ASP A 285	30.026	15.731	25.769	1.00	9.24	8
1031	2150	CG	ASP A 285	33.339	18.591	26.496	1.00	8.25	6
1032	2151	O	ASP A 285	33.394	18.729	25.236	1.00	8.58	8
1033	2152	N	VAL A 286	34.468	18.590	27.218	1.00	7.95	7
1034	2153	CA	VAL A 286	35.413	18.590	27.218	1.00	7.95	7
1035	2154	CG	VAL A 286	35.413	18.590	27.218	1.00	7.95	7
1036	2155	CG	VAL A 286	38.270	19.085	27.261	1.00	5.95	6
1037	2156	CG	VAL A 286	36.418	20.221	28.524	1.00	8.40	6
1038	2157	C	VAL A 286	36.145	17.549	25.719	1.00	7.74	6
1039	2158	O	VAL A 286	36.611	17.833	24.601	1.00	7.94	8
1040	2159	H	PRO A 287	35.967	16.276	26.097	1.00	7.41	7
1041	2160	CG	PRO A 287	35.967	16.276	26.097	1.00	7.41	7
1042	2161	CG	PRO A 287	36.262	15.131	25.326	1.00	7.24	6
1043	2162	CG	PRO A 287	35.802	13.485	25.970	1.00	7.14	6
1044	2163	CG	PRO A 287	35.741	14.357	27.396	1.00	7.12	6
1045	2164	CG	PRO A 287	35.569	15.313	23.873	1.00	7.43	6
1046	2165	O	PRO A 287	36.214	15.113	23.834	1.00	7.51	8
1047	2166	H	LEU A 288	34.293	12.681	25.162	1.00	7.47	7
1048	2167	H	LEU A 288	34.293	12.681	25.162	1.00	7.47	7
1049	2168	CG	LEU A 288	32.169	16.325	22.654	1.00	7.25	6
1050	2169	CG	LEU A 288	31.430	16.185	21.493	1.00	8.35	6
1051	2170	CG	LEU A 288	31.364	15.181	20.494	1.00	8.36	6
1052	2171	CG	LEU A 288	30.038	16.988	21.510	1.00	5.28	6
1053	2172	C	LEU A 288	34.329	16.998	21.722	1.00	7.39	6
1054	2173	H	HIS A 289	34.847	18.097	22.260	1.00	7.34	7
1055	2174	H	HIS A 289	35.583	19.114	21.525	1.00	7.21	6
1056	2175	CG	HIS A 289	36.094	20.260	22.445	1.00	5.61	6
1057	2176	CG	HIS A 289	37.215	21.083	21.882	1.00	5.00	6
1058	2177	CG	HIS A 289	38.548	21.040	22.012	1.00	5.00	6
1059	2178	CG	HIS A 289	38.548	21.040	22.012	1.00	5.00	6
1060	2179	CG	HIS A 289	38.129	22.570	20.527	1.00	5.00	6
1061	2180	CG	HIS A 289	39.124	21.983	21.176	1.00	5.00	7
1062	2181	HE	HIS A 289	36.776	18.507	20.805	1.00	7.52	6
1063	2182	C	HIS A 289	37.083	18.809	19.647	1.00	7.41	8
1064	2183	O	HIS A 289	37.518	17.654	19.545	1.00	7.75	7
1065	2184	N	PHE A 290	38.721	16.971	21.050	1.00	8.12	6
1066	2185	CA	PHE A 290	38.721	16.971	21.050	1.00	8.12	6
1067	2186	CG	PHE A 290	38.721	16.971	21.050	1.00	8.12	6
1068	2187	CG	PHE A 290	38.721	16.971	21.050	1.00	8.12	6
1069	2188	CG	PHE A 290	38.721	16.971	21.050	1.00	8.12	6
1070	2189	CG	PHE A 290	38.721	16.971	21.050	1.00	8.12	6
1071	2190	CG	PHE A 290	38.721	16.971	21.050	1.00	8.12	6
1072	2191	CG	PHE A 290	38.721	16.971	21.050	1.00	8.12	6
1073	2192	CG	PHE A 290	38.721	16.971	21.050	1.00	8.12	6
1074	2193	CG	PHE A 290	38.721	16.971	21.050	1.00	8.12	6
1075	2194	CG	PHE A 290	38.721	16.971	21.050	1.00	8.12	6
1076	2195	CG	PHE A 290	38.721	16.971	21.050	1.00	8.12	6
1077	2196	CG	PHE A 290	38.721	16.971	21.050	1.00	8.12	6
1078	2197	CG	PHE A 290	38.721	16.971	21.050	1.00	8.12	6
1079	2198	CG	PHE A 290	38.721	16.971	21.050	1.00	8.12	6
1080	2199	CG	PHE A 290	38.721	16.971	21.050	1.00	8.12	6
1081	2200	CG	PHE A 290	38.721	16.971	21.050	1.00	8.12	6
1082	2201	CG	PHE A 290	38.721	16.971	21.050	1.00	8.12	6
1083	2202	CG	PHE A 290	38.721	16.971	21.050	1.00	8.12	6
1084	2203	CG	PHE A 290	38.721	16.971	21.050	1.00	8.12	6
1085	2204	CG	PHE A 290	38.721	16.971	21.050	1.00	8.12	6
1086	2205	CG	PHE A 290	38.721	16.971	21.050	1.00	8.12	6
1087	2206	CG	PHE A 290	38.721	16.971	21.050	1.00	8.12	6
1088	2207	CG	PHE A 290	38.721	16.971	21.050	1.00	8.12	6
1089	2208	CG	PHE A 290	38.721	16.971	21.050	1.00	8.12	6
1090	2209	CG	PHE A 290	38.721	16.971	21.050	1.00	8.12	6
1091	2210	CG	PHE A 290	38.721	16.971	21.050	1.00	8.12	6
1092	2211	CG	PHE A 290	38.721	16.971	21.050	1.00	8.12	6
1093	2212	CG	PHE A 290	38.721	16.971	21.050	1.00	8.12	6
1094	2213	CG	PHE A 290	38.721	16.971	21.050	1.00	8.12	6
1095	2214	CG	PHE A 290	38.721	16.971	21.050	1.00	8.12	6
1096	2215	CG	PHE A 290	38.721	16.971	21.050	1.00	8.12	6
1097	2216	CG	PHE A 290	38.721	16.971	21.050	1.00	8.12	6
1098	2217	CG	PHE A 290	38.721	16.971	21.050	1.00	8.12	6
1099	2218	CG	PHE A 290	38.721	16.971	21.050	1.00	8.12	6
1100	2219	CG	PHE A 290	38.721	16.971	21.050	1.00	8.12	6
1101	2220	CG	PHE A 290	38.721	16.971	21.050	1.00	8.12	6
1102	2221	CG	PHE A 290	38.721	16.971	21.050	1.00	8.12	6
1103	2222	CG	PHE A 290	38.721	16.971	21.050	1.00	8.12	6
1104	2223	CG	PHE A 290	38.721	16.971	21.050	1.00	8.12	6
1105	2224	CG	PHE A 290	38.721	16.971	21.050	1.00	8.12	6
1106	2225	CG	PHE A 290	38.721	16.971	21.050	1.00	8.12	6
1107	2226	CG	PHE A 290	38.721	16.971	21.050	1.00	8.12	6
1108	2227	CG	PHE A 290	38.721	16.971	21.050	1.00	8.12	6
1109	2228	CG	PHE A 290	38.721	16.971	21.050	1.00	8.12	6
1110	2229	CG	PHE A 290	38.721	16.971	21.050	1.00	8.12	6
1111	2230	CG	PHE A 290	38.721	16.971	21.050	1.00	8.12	6
1112	2231	CG	PHE A 290	38.721	16.971	21.050	1.00	8.12	6
1113	2232	CG	PHE A 290	38.721	16.971	21.050	1.00	8.12	6
1114	2233	CG	PHE A 290	38.721	16.971	21.050	1.00	8.12	6
1115	2234	CG	PHE A 290	38.721	16.971	21.050	1.00	8.12	6
1116	2235	CG	PHE A 290	38.721	16.971	21.050	1.00	8.12	6
1117	2236	CG	PHE A 290	38.721	16.971	21.050	1.00	8.12	6
1118	2237	CG	PHE A 290	38.721	16.971	21.050	1.00	8.12	6
1119	2238	CG	PHE A 290	38.721	16.971	21.050	1.00	8.12	6
1120	2239	CG	PHE A 290	38.721	16.971	21.050	1.00	8.12	6
1121	2240	CG	PHE A 290	38.721	16.971	21.050	1.00	8.12	6
1122	2241	CG	PHE A 290	38.721	16.971	21.050	1.00	8.12	6
1123	2242	CG	PHE A 290	38.721	16.971	21.050	1.00	8.12	6
1124	2243	CG	PHE A 290	38.721	16.971	21.050	1.00	8.12	6
1125	2244	CG	PHE A 290	38.721	16.971	21.050	1.00	8.12	6
1126	2245	CG	PHE A 290	38.721	16.971	21.050	1.00	8.12	6
1127	2246	CG	PHE A 290	38.721	16.971	21.050	1.00	8.12	6
1128	2247	CG	PHE A 290	38.721	16.971	21.050	1.00	8.12	6
1129	2248	CG	PHE A 290	38.721	16.971	21.050	1.00	8.12	6
1130	2249	CG	PHE A 290	38.721	16.971	21.050	1.00	8.12	6
1131	2250	CG	PHE A 290	38.721	16.971	21.050	1.00	8.12	6
1132	2251	CG	PHE A 290	38.721	16.971	21.050	1.00	8.12	6
1133	2252	CG	PHE A 290	38.721	16.971	21.050	1.00	8.12	6
1134	2253	CG	PHE A 290	38.721	16.971	21.050	1.00	8.12	6
1135	2254	CG	PHE A 290	38.721	16.971	21.050	1.00	8.12	6
1136	2255	CG	PHE A 290	38.721	16.971	21.050	1.00	8.12	6
1137	2256	CG	PHE A 290	38.721	16.971	21.050	1.00	8.12	6
1138	2257	CG	PHE A 290	38.721	16.971	21.050	1.00	8.12	6
1139	2258	CG	PHE A 290	38.721	16.971	21.050	1.00	8.12	6
1140	2259	CG							

ATOM	2439	OG	SEA	A	297	18.303	13.176	1.00	10.20	24	6
ATOM	2440	C	SEA	A	297	16.146	10.508	1.00	15.90	6	6
ATOM	2441	C	SEA	A	297	16.146	10.508	1.00	15.90	6	6
ATOM	2442	C	SEA	A	298	15.724	10.372	1.00	16.31	7	6
ATOM	2443	C	SEA	A	298	15.724	10.372	1.00	16.31	7	6
ATOM	2444	C	SEA	A	298	13.080	9.722	1.00	16.82	7	6
ATOM	2445	C	SEA	A	298	12.457	10.523	1.00	18.92	6	6
ATOM	2446	C	SEA	A	298	12.457	10.523	1.00	18.92	6	6
ATOM	2447	C	SEA	A	298	12.457	10.523	1.00	18.92	6	6
ATOM	2448	C	SEA	A	298	12.457	10.523	1.00	18.92	6	6
ATOM	2449	C	SEA	A	298	12.457	10.523	1.00	18.92	6	6
ATOM	2450	C	SEA	A	298	12.457	10.523	1.00	18.92	6	6
ATOM	2451	C	SEA	A	299	11.907	14.913	1.00	16.90	7	6
ATOM	2452	C	SEA	A	299	11.907	14.913	1.00	16.90	7	6
ATOM	2453	C	SEA	A	299	11.907	14.913	1.00	16.90	7	6
ATOM	2454	C	SEA	A	299	11.907	14.913	1.00	16.90	7	6
ATOM	2455	C	SEA	A	300	10.855	13.274	1.00	16.11	7	6
ATOM	2456	C	SEA	A	300	10.855	13.274	1.00	16.11	7	6
ATOM	2457	C	SEA	A	300	10.855	13.274	1.00	16.11	7	6
ATOM	2458	C	SEA	A	300	10.855	13.274	1.00	16.11	7	6
ATOM	2459	C	SEA	A	301	10.855	13.274	1.00	16.11	7	6
ATOM	2460	C	SEA	A	301	10.855	13.274	1.00	16.11	7	6
ATOM	2461	C	SEA	A	301	10.855	13.274	1.00	16.11	7	6
ATOM	2462	C	SEA	A	301	10.855	13.274	1.00	16.11	7	6
ATOM	2463	C	SEA	A	302	10.855	13.274	1.00	16.11	7	6
ATOM	2464	C	SEA	A	302	10.855	13.274	1.00	16.11	7	6
ATOM	2465	C	SEA	A	302	10.855	13.274	1.00	16.11	7	6
ATOM	2466	C	SEA	A	302	10.855	13.274	1.00	16.11	7	6
ATOM	2467	C	SEA	A	302	10.855	13.274	1.00	16.11	7	6
ATOM	2468	C	SEA	A	302	10.855	13.274	1.00	16.11	7	6
ATOM	2469	C	SEA	A	302	10.855	13.274	1.00	16.11	7	6
ATOM	2470	C	SEA	A	302	10.855	13.274	1.00	16.11	7	6
ATOM	2471	C	SEA	A	302	10.855	13.274	1.00	16.11	7	6
ATOM	2472	C	SEA	A	302	10.855	13.274	1.00	16.11	7	6
ATOM	2473	C	SEA	A	302	10.855	13.274	1.00	16.11	7	6
ATOM	2474	C	SEA	A	302	10.855	13.274	1.00	16.11	7	6
ATOM	2475	C	SEA	A	303	10.855	13.274	1.00	16.11	7	6
ATOM	2476	C	SEA	A	303	10.855	13.274	1.00	16.11	7	6
ATOM	2477	C	SEA	A	303	10.855	13.274	1.00	16.11	7	6
ATOM	2478	C	SEA	A	303	10.855	13.274	1.00	16.11	7	6
ATOM	2479	C	SEA	A	303	10.855	13.274	1.00	16.11	7	6
ATOM	2480	C	SEA	A	303	10.855	13.274	1.00	16.11	7	6
ATOM	2481	C	SEA	A	303	10.855	13.274	1.00	16.11	7	6
ATOM	2482	C	SEA	A	303	10.855	13.274	1.00	16.11	7	6
ATOM	2483	C	SEA	A	303	10.855	13.274	1.00	16.11	7	6
ATOM	2484	C	SEA	A	303	10.855	13.274	1.00	16.11	7	6
ATOM	2485	C	SEA	A	304	10.855	13.274	1.00	16.11	7	6
ATOM	2486	C	SEA	A	304	10.855	13.274	1.00	16.11	7	6
ATOM	2487	C	SEA	A	304	10.855	13.274	1.00	16.11	7	6
ATOM	2488	C	SEA	A	304	10.855	13.274	1.00	16.11	7	6
ATOM	2489	C	SEA	A	304	10.855	13.274	1.00	16.11	7	6
ATOM	2490	C	SEA	A	304	10.855	13.274	1.00	16.11	7	6
ATOM	2491	C	SEA	A	305	10.855	13.274	1.00	16.11	7	6

25.45	ATHM	25.45	O	THR A 311	30.467	10.902	27.258	1.00	11.29	8
25.46	ATHM	25.46	H	VAL A 312	30.313	13.282	27.645	1.00	11.29	6
25.47	ATHM	25.47	H	VAL A 313	30.367	13.085	27.605	1.00	11.29	6
25.48	ATHM	25.48	CB	VAL A 312	29.620	14.906	30.597	1.00	12.62	6
25.49	ATHM	25.49	CG2	VAL A 312	31.995	14.730	29.912	1.00	10.56	6
25.50	ATHM	25.50	CG2	VAL A 312	28.853	13.189	28.191	1.00	11.23	6
25.51	ATHM	25.51	O	VAL A 313	29.203	13.825	27.604	1.00	11.42	7
25.52	ATHM	25.52	H	VAL A 313	29.533	13.790	27.491	1.00	11.42	6
25.53	ATHM	25.53	M	VAL A 313	27.208	13.820	26.498	1.00	11.94	6
25.54	ATHM	25.54	CB	VAL A 313	27.107	14.723	25.265	1.00	12.88	6
25.55	ATHM	25.55	CB	VAL A 313	27.604	14.175	23.942	1.00	13.31	6
25.56	ATHM	25.56	CG2	VAL A 313	26.655	13.102	25.100	1.00	11.96	6
25.57	ATHM	25.57	CG2	VAL A 313	26.655	13.102	25.100	1.00	11.96	6
25.58	ATHM	25.58	H	VAL A 313	25.434	12.216	26.319	1.00	11.69	6
25.59	ATHM	25.59	O	VAL A 313	25.434	12.216	26.319	1.00	11.69	6
25.60	ATHM	25.60	H	VAL A 313	27.418	11.311	25.971	1.00	12.83	7
25.61	ATHM	25.61	CA	SER A 314	26.878	9.987	25.000	1.00	13.56	6
25.62	ATHM	25.62	CA	SER A 314	27.801	9.954	24.922	1.00	13.63	6
25.63	ATHM	25.63	CG	VAL A 314	26.929	9.048	27.464	1.00	15.90	8
25.64	ATHM	25.64	CG	VAL A 314	26.929	9.048	27.464	1.00	15.90	8
25.65	ATHM	25.65	O	VAL A 314	25.710	8.445	27.105	1.00	14.28	8
25.66	ATHM	25.66	H	VAL A 315	27.168	9.725	28.254	1.00	14.22	6
25.67	ATHM	25.67	CA	LVS A 315	26.823	9.081	29.513	1.00	14.22	6
25.68	ATHM	25.68	CB	LVS A 315	27.928	8.797	30.491	1.00	19.81	6
25.69	ATHM	25.69	CG	LVS A 315	30.331	10.319	30.319	1.00	26.75	6
25.70	ATHM	25.70	CG	LVS A 315	30.331	10.319	30.319	1.00	26.75	6
25.71	ATHM	25.71	CE	LVS A 315	30.716	11.312	31.825	1.00	35.30	6
25.72	ATHM	25.72	NZ	LVS A 315	31.599	9.199	32.634	1.00	35.37	7
25.73	ATHM	25.73	O	LVS A 315	25.684	9.951	30.379	1.00	13.42	6
25.74	ATHM	25.74	O	LVS A 315	26.969	9.435	31.020	1.00	13.42	8
25.75	ATHM	25.75	H	VAL A 316	26.100	11.257	30.397	1.00	13.42	7
25.76	ATHM	25.76	CA	THR A 322	26.302	12.797	31.327	1.00	13.02	6
25.77	ATHM	25.77	CB	HIS A 316	26.530	11.718	31.313	1.00	12.94	6
25.78	ATHM	25.78	CG2	HIS A 316	25.796	11.024	34.166	1.00	13.25	6
25.79	ATHM	25.79	CG2	HIS A 316	27.835	11.194	33.424	1.00	15.42	7
25.80	ATHM	25.80	MO1	HIS A 316	27.850	10.206	34.317	1.00	14.97	6
25.81	ATHM	25.81	CE1	HIS A 316	26.669	13.106	34.822	1.00	15.47	7
25.82	ATHM	25.82	CE2	HIS A 316	26.669	13.106	34.822	1.00	15.47	7
25.83	ATHM	25.83	O	HIS A 316	25.304	13.079	30.471	1.00	12.59	6
25.84	ATHM	25.84	H	VAL A 317	23.668	14.725	29.431	1.00	12.52	7
25.85	ATHM	25.85	N	PRO A 317	23.256	11.740	29.268	1.00	12.43	6
25.86	ATHM	25.86	CD	PRO A 317	23.256	11.740	29.268	1.00	12.50	6
25.87	ATHM	25.87	CA	PRO A 317	23.311	14.940	29.519	1.00	12.50	6
25.88	ATHM	25.88	CG	PRO A 317	21.998	12.055	28.654	1.00	12.54	6
25.89	ATHM	25.89	CG	PRO A 317	21.998	12.055	28.654	1.00	12.54	6
25.90	ATHM	25.90	O	PRO A 317	22.669	15.253	29.133	1.00	12.59	6
25.91	ATHM	25.91	O	PRO A 317	22.750	16.349	28.282	1.00	12.88	8
25.92	ATHM	25.92	N	LEU A 318	22.033	15.168	30.285	1.00	12.44	7
25.93	ATHM	25.93	CA	LEU A 318	21.370	16.286	30.956	1.00	12.77	6
25.94	ATHM	25.94	CG	LEU A 318	19.526	15.805	31.703	1.00	13.88	6
25.95	ATHM	25.95	CG	LEU A 318	19.526	15.805	31.703	1.00	13.88	6
25.96	ATHM	25.96	CG1	LEU A 318	18.520	16.143	32.241	1.00	15.19	6
25.97	ATHM	25.97	CG2	LEU A 318	18.520	16.143	32.241	1.00	15.19	6
25.98	ATHM	25.98	O	LEU A 318	22.338	17.175	31.741	1.00	11.91	6
25.99	ATHM	25.99	O	LEU A 318	21.402	16.757	31.658	1.00	11.31	7
26.00	ATHM	26.00	H	VAL A 319	24.559	17.559	32.591	1.00	11.24	6
26.01	ATHM	26.01	CA	LVS A 319	25.135	17.559	32.591	1.00	11.24	6
26.02	ATHM	26.02	CA	LVS A 319	24.001	16.369	34.812	1.00	12.23	6
26.03	ATHM	26.03	CG	LVS A 319	23.455	17.705	35.070	1.00	13.91	6
26.04	ATHM	26.04	CG	LVS A 319	22.335	17.774	36.181	1.00	14.09	7
26.05	ATHM	26.05	NZ	LVS A 319	25.455	17.705	35.070	1.00	14.09	7
26.06	ATHM	26.06	NZ	LVS A 319	25.455	17.705	35.070	1.00	14.09	7
26.07	ATHM	26.07	O	LVS A 319	26.717	18.088	31.440	1.00	11.10	8
26.08	ATHM	26.08	H	VAL A 320	26.717	18.376	32.153	1.00	10.24	7
26.09	ATHM	26.09	H	VAL A 320	25.462	17.969	30.320	1.00	10.24	7
26.10	ATHM	26.10	CA	SER A 320	26.564	18.409	29.483	1.00	9.74	6
26.11	ATHM	26.11	CA	SER A 320	26.825	17.443	28.311	1.00	11.44	6
26.12	ATHM	26.12	CG	VAL A 320	26.329	19.681	28.982	1.00	9.00	8
26.13	ATHM	26.13	CG	VAL A 320	26.329	19.681	28.982	1.00	9.00	8
26.14	ATHM	26.14	O	VAL A 321	25.215	19.672	28.144	1.00	9.21	6
26.15	ATHM	26.15	H	VAL A 321	27.294	20.549	28.581	1.00	8.35	7
26.16	ATHM	26.16	CA	VAL A 321	27.166	21.744	27.760	1.00	7.87	6
26.17	ATHM	26.17	CA	VAL A 321	27.455	23.005	28.427	1.00	6.55	6
26.18	ATHM	26.18	CG	VAL A 321	27.455	23.005	28.427	1.00	6.55	6
26.19	ATHM	26.19	CG2	VAL A 321	28.076	21.422	26.585	1.00	7.75	6
26.20	ATHM	26.20	CG2	VAL A 321	28.076	21.422	26.585	1.00	7.75	6
26.21	ATHM	26.21	O	VAL A 321	29.282	21.166	26.791	1.00	8.04	8
26.22	ATHM	26.22	CA	THR A 322	27.497	21.399	25.396	1.00	7.46	7
26.23	ATHM	26.23	CA	THR A 322	28.302	21.038	24.183	1.00	7.12	6
26.24	ATHM	26.24	CG	THR A 322	27.504	20.146	23.999	1.00	5.50	6
26.25	ATHM	26.25	CG	THR A 322	27.504	20.146	23.999	1.00	5.50	6
26.26	ATHM	26.26	CG2	THR A 322	29.376	20.559	25.923	1.00	5.00	8
26.27	ATHM	26.27	O	THR A 322	28.877	22.242	23.082	1.00	7.18	6
26.28	ATHM	26.28	O	THR A 322	28.206	23.319	23.510	1.00	7.34	8
26.29	ATHM	26.29	N	PHE A 323	30.076	22.181	22.907	1.00	6.79	7
26.30	ATHM	26.30	N	PHE A 323	30.734	23.301	22.257	1.00	6.58	6
26.31	ATHM	26.31	CA	PHE A 323	31.435	24.192	23.312	1.00	5.72	6
26.32	ATHM	26.32	CA	PHE A 323	31.435	24.192	23.312	1.00	5.72	6
26.33	ATHM	26.33	CG1	PHE A 323	32.912	22.783	23.049	1.00	6.41	6
26.34	ATHM	26.34	CG1	PHE A 323	32.912	22.783	23.049	1.00	6.41	6
26.35	ATHM	26.35	CE1	PHE A 323	35.167	23.880	23.764	1.00	7.34	6
26.36	ATHM	26.36	CE2	PHE A 323	35.167	23.880	23.764	1.00	7.34	6
26.37	ATHM	26.37	CE2	PHE A 323	34.105	22.368	25.353	1.00	6.00	6
26.38	ATHM	26.38	CE2	PHE A 323	34.105	22.368	25.353	1.00	6.00	6
26.39	ATHM	26.39	O	PHE A 324	31.727	22.855	21.184	1.00	6.75	6
26.40	ATHM	26.40	H	VAL A 324	31.917	23.742	20.742	1.00	6.74	8
26.41	ATHM	26.41	CA	VAL A 324	32.464	23.539	19.087	1.00	6.92	6
26.42	ATHM	26.42	CA	VAL A 324	32.464	23.539	19.087	1.00	6.92	6
26.43	ATHM	26.43	CG1	VAL A 324	30.145	23.923	16.959	1.00	5.00	6
26.44	ATHM	26.44	CG1	VAL A 324	30.145	23.923	16.959	1.00	5.00	6
26.45	ATHM	26.45	CG2	VAL A 324	35.247	21.177	19.534	1.00	7.23	6
26.46	ATHM	26.46	H	VAL A 325	35.247	21.177	19.534	1.00	7.23	6
26.47	ATHM	26.47	N	ASP A 325	34.276	25.479	19.678	1.00	7.59	7
26.48	ATHM	26.48	CB	ASP A 325	35.469	26.899	20.978	1.00	7.78	6
26.49	ATHM	26.49	CG	ASP A 325	36.180	26.899	20.978	1.00	8.42	6
26.50	ATHM	26.50	CG	ASP A 325	37.157	25.954	18.192	1.00	8.81	6

2651	001	ASP	A	325	36.076	25.409	10.439	1.00	7.66	8
2652	002	ASP	A	325	37.027	25.682	16.964	1.00	9.34	8
2653	003	ASP	A	325	35.117	27.261	21.116	1.00	8.18	6
2654	0	ASP	A	325	35.117	27.261	21.116	1.00	8.18	6
2655	0	ASP	A	326	33.900	27.685	21.254	1.00	8.16	8
2656	0	ASP	A	326	36.100	27.788	21.426	1.00	8.35	7
2657	001	ASP	A	326	32.487	28.329	24.000	1.00	9.54	6
2658	002	ASP	A	326	36.502	27.485	24.902	1.00	11.91	6
2659	003	ASP	A	326	37.071	27.415	24.622	1.00	12.52	8
2660	004	ASP	A	326	36.121	26.782	25.965	1.00	11.95	7
2661	0	ASP	A	326	37.212	29.685	22.871	1.00	9.78	6
2662	0	ASP	A	327	37.212	29.685	22.871	1.00	9.78	6
2663	001	ASP	A	327	37.260	30.626	23.534	1.00	8.65	7
2664	002	ASP	A	327	38.367	31.562	23.994	1.00	9.17	6
2665	003	ASP	A	327	37.976	32.718	26.999	1.00	8.48	6
2666	004	ASP	A	327	37.800	32.154	26.392	1.00	7.81	6
2667	001	ASP	A	327	38.781	31.222	26.392	1.00	8.48	6
2668	002	ASP	A	327	38.781	31.222	26.392	1.00	8.48	6
2669	003	ASP	A	327	36.886	30.856	27.951	1.00	7.98	6
2670	004	ASP	A	327	37.083	31.538	28.493	1.00	8.30	7
2671	0	ASP	A	327	39.664	30.866	24.404	1.00	9.58	6
2672	0	ASP	A	327	40.718	31.444	24.169	1.00	9.63	8
2673	0	ASP	A	328	39.645	29.653	24.328	1.00	10.01	7
2674	001	ASP	A	328	40.422	29.735	24.311	1.00	10.42	6
2675	002	ASP	A	328	40.422	29.735	24.311	1.00	10.42	6
2676	003	ASP	A	328	39.676	27.936	27.629	1.00	10.50	6
2677	004	ASP	A	328	40.162	28.843	28.365	1.00	17.22	8
2678	001	ASP	A	328	38.615	27.265	28.055	1.00	16.97	8
2679	002	ASP	A	328	41.385	28.188	24.074	1.00	10.65	6
2680	003	ASP	A	329	40.518	27.688	23.167	1.00	10.42	7
2681	004	ASP	A	329	40.518	27.688	23.167	1.00	10.42	7
2682	0	ASP	A	329	40.946	26.860	22.028	1.00	10.37	6
2683	001	ASP	A	329	39.933	25.709	21.777	1.00	10.26	6
2684	002	ASP	A	329	38.709	26.293	21.286	1.00	9.63	8
2685	003	ASP	A	329	37.506	25.273	23.020	1.00	9.29	6
2686	004	ASP	A	329	37.506	25.273	23.020	1.00	9.29	6
2687	0	ASP	A	329	41.563	26.599	19.702	1.00	9.96	8
2688	001	ASP	A	330	40.827	28.078	20.679	1.00	10.77	7
2689	002	ASP	A	330	40.985	29.668	19.441	1.00	11.30	6
2690	003	ASP	A	330	40.182	30.988	19.518	1.00	9.13	6
2691	004	ASP	A	330	40.769	31.987	20.543	1.00	8.40	6
2692	001	ASP	A	330	39.089	31.369	21.393	1.00	7.21	6
2693	002	ASP	A	330	40.432	34.237	19.660	1.00	7.16	7
2694	003	ASP	A	330	42.486	29.890	19.121	1.00	11.99	6
2695	004	ASP	A	330	43.345	29.690	20.092	1.00	11.79	8
2696	0	ASP	A	331	42.793	30.208	17.963	1.00	12.80	8
2697	001	ASP	A	331	44.119	30.322	17.442	1.00	13.55	6
2698	002	ASP	A	331	44.119	30.322	17.442	1.00	13.55	6
2699	003	ASP	A	331	42.608	30.336	15.966	1.00	13.53	6
2700	004	ASP	A	331	42.608	30.336	15.966	1.00	13.10	6
2701	0	ASP	A	331	44.899	31.372	18.320	1.00	14.55	8
2702	0	ASP	A	331	44.899	31.372	18.320	1.00	14.55	8
2703	0	ASP	A	331	44.496	32.463	18.767	1.00	14.46	8
2704	0	ASP	A	332	46.122	30.893	18.593	1.00	15.77	7
2705	001	ASP	A	332	47.087	31.624	19.404	1.00	17.06	6
2706	002	ASP	A	332	46.081	31.453	20.896	1.00	18.22	6
2707	003	ASP	A	332	45.755	30.962	21.523	1.00	19.06	8
2708	004	ASP	A	332	45.755	30.962	21.523	1.00	19.06	8
2709	0	ASP	A	333	45.670	30.778	22.875	1.00	19.88	6
2710	001	ASP	A	333	44.181	30.538	23.241	1.00	19.70	6
2711	002	ASP	A	333	43.711	32.283	23.072	1.00	20.78	6
2712	003	ASP	A	333	44.572	33.254	23.876	1.00	23.47	8
2713	004	ASP	A	333	45.181	34.191	23.715	1.00	25.12	8
2714	0	ASP	A	333	46.422	34.252	24.442	1.00	25.12	8
2715	001	ASP	A	333	46.422	34.252	24.442	1.00	25.12	8
2716	002	ASP	A	333	47.167	29.822	23.773	1.00	20.84	8
2717	003	ASP	A	334	46.339	29.555	24.795	1.00	21.65	7
2718	004	ASP	A	334	47.083	28.519	25.552	1.00	22.42	6
2719	0	ASP	A	334	45.405	28.099	27.335	1.00	22.42	6
2720	001	ASP	A	334	46.700	27.074	25.194	1.00	30.83	8
2721	002	ASP	A	334	47.687	26.293	24.929	1.00	22.55	8
2722	003	ASP	A	334	45.506	26.728	25.170	1.00	21.74	7
2723	004	ASP	A	334	44.958	25.411	24.863	1.00	20.75	6
2724	0	ASP	A	335	43.814	25.183	25.883	1.00	22.84	6
2725	001	ASP	A	335	43.814	25.183	25.883	1.00	22.84	6
2726	002	ASP	A	335	43.065	25.298	26.305	1.00	23.07	6
2727	003	ASP	A	335	43.065	25.298	26.305	1.00	23.07	6
2728	004	ASP	A	335	45.184	24.089	27.673	1.00	24.51	6
2729	0	ASP	A	335	44.460	25.313	23.427	1.00	19.68	6
2730	001	ASP	A	335	43.491	24.609	23.136	1.00	19.77	8
2731	002	ASP	A	335	45.111	26.053	22.536	1.00	18.47	7
2732	003	ASP	A	336	44.766	26.089	21.169	1.00	17.45	6
2733	004	ASP	A	336	45.405	26.544	18.905	1.00	22.99	6
2734	0	ASP	A	336	45.405	26.544	18.905	1.00	22.99	6
2735	001	ASP	A	336	46.508	27.440	18.036	1.00	26.38	6
2736	002	ASP	A	336	47.378	28.166	18.504	1.00	26.94	8
2737	003	ASP	A	336	46.276	27.487	16.805	1.00	28.18	8
2738	004	ASP	A	336	44.504	24.698	20.571	1.00	16.40	6
2739	0	ASP	A	336	44.504	24.698	20.571	1.00	16.40	6
2740	001	ASP	A	337	43.338	23.527	19.967	1.00	16.97	9
2741	002	ASP	A	337	43.338	23.527	19.967	1.00	16.97	9
2742	003	ASP	A	337	42.891	22.175	20.487	1.00	13.48	6
2743	004	ASP	A	337	41.855	22.515	21.439	1.00	13.96	8
2744	0	ASP	A	337	41.679	23.436	18.465	1.00	13.62	6
2745	001	ASP	A	337	40.615	22.864	18.896	1.00	13.37	8
2746	002	ASP	A	337	40.615	22.864	18.896	1.00	13.37	8
2747	003	ASP	A	338	40.800	24.636	16.837	1.00	13.74	7
2748	004	ASP	A	338	41.340	26.036	16.033	1.00	13.02	6
2749	001	ASP	A	338	41.955	26.036	17.006	1.00	14.55	8
2750	002	ASP	A	338	40.259	26.796	15.338	1.00	12.29	6
2751	003	ASP	A	338	40.216	23.770	15.877	1.00	13.20	6
2752	004	ASP	A	338	38.905	22.766	14.781	1.00	13.26	8
2753	0	ASP	A	339	38.905	22.766	14.781	1.00	13.26	8
2754	001	ASP	A	339	38.270	22.857	14.783	1.00	12.62	6
2755	002	ASP	A	339	36.803	22.594	15.154	1.00	11.55	6
2756	003	ASP	A	339	36.030	21.874	14.057	1.00	9.87	6

2757	CG2	VAL	A	339	36.745	21.811	16.483	1.00	9.286	6
2758	CG2	VAL	A	339	36.513	23.484	13.385	1.00	12.537	6
2759	CG2	VAL	A	339	36.271	25.466	12.600	1.00	12.537	6
2760	CG2	VAL	A	339	36.029	27.448	11.816	1.00	12.537	6
2761	CG1	G14	A	340	39.280	23.302	11.088	1.00	12.555	6
2762	CG1	G14	A	340	39.075	22.357	10.097	1.00	11.111	6
2763	CG1	G14	A	340	41.372	21.974	9.559	1.00	11.555	6
2764	CG1	G14	A	340	42.073	21.105	9.513	1.00	16.34	6
2765	CG1	G14	A	340	41.594	20.002	8.384	1.00	15.11	7
2766	CG1	G14	A	340	41.594	20.002	8.384	1.00	15.11	7
2767	CG1	G14	A	340	38.009	21.000	10.648	1.00	12.34	6
2768	D	H18	A	341	36.930	23.331	10.565	1.00	12.28	6
2769	D	H18	A	341	36.147	25.042	9.779	1.00	12.25	7
2770	CA	H18	A	341	37.024	25.755	9.200	1.00	12.38	6
2771	CA	H18	A	341	38.516	26.753	8.385	1.00	12.36	6
2772	CA	H18	A	341	38.516	26.753	8.385	1.00	12.36	6
2773	CG2	H18	A	341	36.347	27.484	7.716	1.00	14.77	6
2774	CA	H18	A	341	36.124	24.916	8.332	1.00	12.08	6
2775	D	H18	A	341	34.910	25.018	8.411	1.00	12.16	8
2776	N	H18	A	342	36.608	24.095	7.465	1.00	11.85	7
2777	CA	H18	A	342	35.902	23.225	6.395	1.00	11.19	6
2778	CA	H18	A	342	35.902	23.225	6.395	1.00	11.19	6
2779	CG1	H18	A	342	37.568	21.288	6.392	1.00	9.86	6
2780	CG2	H18	A	342	37.073	19.949	6.491	1.00	9.37	6
2781	CG2	H18	A	342	37.908	19.219	7.276	1.00	10.97	6
2782	CE1	H18	A	342	35.916	19.290	5.991	1.00	10.12	6
2783	CG1	H18	A	342	35.756	21.330	7.062	1.00	10.06	6
2784	CG1	H18	A	342	35.756	21.330	7.062	1.00	10.06	6
2785	CG1	H18	A	342	37.069	19.880	7.532	1.00	10.51	7
2786	CG1	H18	A	342	35.700	17.950	6.293	1.00	9.23	6
2787	CG2	H18	A	342	36.634	17.222	7.030	1.00	10.34	6
2788	CG1	H18	A	342	34.968	22.340	7.391	1.00	10.76	6
2789	D	H18	A	342	35.037	22.038	6.990	1.00	10.60	8
2790	CA	H18	A	342	35.321	21.916	6.977	1.00	10.45	7
2791	CA	H18	A	342	35.321	21.916	6.977	1.00	10.45	7
2792	CG1	H18	A	343	35.520	20.880	10.193	1.00	10.59	6
2793	CG1	H18	A	343	34.641	18.808	10.796	1.00	10.94	6
2794	CG1	H18	A	343	34.561	17.786	9.989	1.00	9.97	6
2795	CG2	H18	A	343	34.666	18.875	12.117	1.00	9.30	6
2796	CG1	H18	A	343	33.746	16.653	10.569	1.00	10.66	6
2797	CG1	H18	A	343	33.746	16.653	10.569	1.00	10.66	6
2798	CG1	H18	A	343	33.592	16.537	11.865	1.00	10.55	6
2799	CG1	H18	A	343	33.621	21.720	10.332	1.00	9.65	6
2800	D	H18	A	343	32.649	21.160	10.826	1.00	9.50	8
2801	N	L15	A	344	33.897	23.010	10.569	1.00	9.52	7
2802	CG1	L15	A	344	33.084	23.775	11.536	1.00	9.73	6
2803	CG1	L15	A	344	33.084	23.775	11.536	1.00	9.73	6
2804	CG1	L15	A	344	33.193	25.978	12.846	1.00	11.02	6
2805	CG1	L15	A	344	34.235	26.994	13.366	1.00	10.40	6
2806	CG1	L15	A	344	35.068	26.281	14.470	1.00	9.19	6
2807	N2	L15	A	344	36.098	27.262	14.962	1.00	7.52	7
2808	CG1	L15	A	344	31.573	23.696	11.394	1.00	9.62	6
2809	D	L15	A	344	30.330	23.428	12.371	1.00	9.63	8
2810	N	PRO	A	345	28.110	20.031	14.671	1.00	7.06	6
2811	CG1	PRO	A	345	28.712	20.558	15.670	1.00	7.03	8
2812	CG1	PRO	A	345	28.712	20.558	15.670	1.00	7.03	8
2813	CG1	PRO	A	345	28.712	20.558	15.670	1.00	7.03	8
2814	CG1	PRO	A	345	28.712	20.558	15.670	1.00	7.03	8
2815	CG1	PRO	A	345	28.712	20.558	15.670	1.00	7.03	8
2816	CG1	PRO	A	345	28.712	20.558	15.670	1.00	7.03	8
2817	CG1	PRO	A	345	28.712	20.558	15.670	1.00	7.03	8
2818	CG1	PRO	A	345	28.712	20.558	15.670	1.00	7.03	8
2819	CG1	PRO	A	345	28.712	20.558	15.670	1.00	7.03	8
2820	CG1	PRO	A	345	28.712	20.558	15.670	1.00	7.03	8
2821	CG1	PRO	A	345	28.712	20.558	15.670	1.00	7.03	8
2822	CG1	PRO	A	345	28.712	20.558	15.670	1.00	7.03	8
2823	CG1	PRO	A	345	28.712	20.558	15.670	1.00	7.03	8
2824	CG1	PRO	A	345	28.712	20.558	15.670	1.00	7.03	8
2825	CG1	PRO	A	345	28.712	20.558	15.670	1.00	7.03	8
2826	CG1	PRO	A	345	28.712	20.558	15.670	1.00	7.03	8
2827	CG1	PRO	A	345	28.712	20.558	15.670	1.00	7.03	8
2828	CG1	PRO	A	345	28.712	20.558	15.670	1.00	7.03	8
2829	CG1	PRO	A	345	28.712	20.558	15.670	1.00	7.03	8
2830	CG1	PRO	A	345	28.712	20.558	15.670	1.00	7.03	8
2831	CG1	PRO	A	345	28.712	20.558	15.670	1.00	7.03	8
2832	CG1	PRO	A	345	28.712	20.558	15.670	1.00	7.03	8
2833	CG1	PRO	A	345	28.712	20.558	15.670	1.00	7.03	8
2834	CG1	PRO	A	345	28.712	20.558	15.670	1.00	7.03	8
2835	CG1	PRO	A	345	28.712	20.558	15.670	1.00	7.03	8
2836	CG1	PRO	A	345	28.712	20.558	15.670	1.00	7.03	8
2837	CG1	PRO	A	345	28.712	20.558	15.670	1.00	7.03	8
2838	CG1	PRO	A	345	28.712	20.558	15.670	1.00	7.03	8
2839	CG1	PRO	A	345	28.712	20.558	15.670	1.00	7.03	8
2840	CG1	PRO	A	345	28.712	20.558	15.670	1.00	7.03	8
2841	CG1	PRO	A	345	28.712	20.558	15.670	1.00	7.03	8
2842	CG1	PRO	A	345	28.712	20.558	15.670	1.00	7.03	8
2843	CG1	PRO	A	345	28.712	20.558	15.670	1.00	7.03	8
2844	CG1	PRO	A	345	28.712	20.558	15.670	1.00	7.03	8
2845	CG1	PRO	A	345	28.712	20.558	15.670	1.00	7.03	8
2846	CG1	PRO	A	345	28.712	20.558	15.670	1.00	7.03	8
2847	CG1	PRO	A	345	28.712	20.558	15.670	1.00	7.03	8
2848	CG1	PRO	A	345	28.712	20.558	15.670	1.00	7.03	8
2849	CG1	PRO	A	345	28.712	20.558	15.670	1.00	7.03	8
2850	CG1	PRO	A	345	28.712	20.558	15.670	1.00	7.03	8
2851	CG1	PRO	A	345	28.712	20.558	15.670	1.00	7.03	8
2852	CG1	PRO	A	345	28.712	20.558	15.670	1.00	7.03	8
2853	CG1	PRO	A	345	28.712	20.558	15.670	1.00	7.03	8
2854	CG1	PRO	A	345	28.712	20.558	15.670	1.00	7.03	8
2855	CG1	PRO	A	345	28.712	20.558	15.670	1.00	7.03	8
2856	CG1	PRO	A	345	28.712	20.558	15.670	1.00	7.03	8
2857	CG1	PRO	A	345	28.712	20.558	15.670	1.00	7.03	8
2858	CG1	PRO	A	345	28.712	20.558	15.670	1.00	7.03	8
2859	CG1	PRO	A	345	28.712	20.558	15.670	1.00	7.03	8
2860	CG1	PRO	A	345	28.712	20.558	15.670	1.00	7.03	8
2861	CG1	PRO	A	345	28.712	20.558	15.670	1.00	7.03	8
2862	CG1	PRO	A	345	28.712	20.558	15.670	1.00	7.03	8
2863	CG1	PRO	A	345	28.712	20.558	15.670	1.00	7.03	8
2864	CG1	PRO	A	345	28.712	20.558	15.670	1.00	7.03	8
2865	CG1	PRO	A	345	28.712	20.558	15.670	1.00	7.03	8
2866	CG1	PRO	A	345	28.712	20.558	15.670	1.00	7.03	8
2867	CG1	PRO	A	345	28.712	20.558	15.670	1.00	7.03	8
2868	CG1	PRO	A	345	28.712	20.558	15.670	1.00	7.03	8
2869	CG1	PRO	A	345	28.712	20.558	15.670	1.00	7.03	8
2870	CG1	PRO	A	345	28.712	20.558	15.670	1.00	7.03	8
2871	CG1	PRO	A	345	28.712	20.558	15.670	1.00	7.03	8
2872	CG1	PRO	A	345	28.712	20.558	15.670	1.00	7.03	8
2873	CG1	PRO	A	345	28.712	20.558	15.670	1.00	7.03	8
2874	CG1	PRO	A	345	28.712	20.558	15.670	1.00	7.03	8
2875	CG1	PRO	A	345	28.712	20.558	15.670	1.00	7.03	8
2876	CG1	PRO	A	345	28.712	20.558	15.670	1.00	7.03	8
2877	CG1	PRO	A	345	28.712	20.558	15.670	1.00	7.03	8
2878	CG1	PRO	A	345	28.712	20.558	15.670	1.00	7.03	8
2879	CG1	PRO	A	345	28.712	20.558	15.670	1.00	7.03	8
2880	CG1	PRO	A	345	28.712	20.558	15.670	1.00	7.03	8
2881	CG1	PRO	A	345	28.712	20.558	15.670	1.00	7.03	8
2882	CG1	PRO	A	345	28.712	20.558	15.670	1.0		



1969	N	GLY A 364	33.399	34.040	10.452	1.00	8.56	7
1970	CA	GLY A 364	34.472	34.061	17.503	1.00	8.01	6
1971	C	GLY A 364	34.083	33.261	16.231	1.00	9.84	6
1972	O	GLY A 364	34.506	33.639	15.156	1.00	8.91	8
1973	O	GLY A 365	33.233	32.251	16.237	1.00	9.21	7
1974	CA	GLY A 365	32.255	31.113	15.120	1.00	8.93	6
1975	CA	GLY A 365	32.255	31.113	15.120	1.00	8.93	6
1976	CA	GLY A 365	33.349	29.235	15.977	1.00	9.58	6
1977	CA	GLY A 365	34.516	29.232	15.641	1.00	10.56	8
1978	CA	GLY A 365	33.078	28.275	16.700	1.00	9.75	8
1979	C	GLY A 365	31.780	32.264	14.321	1.00	10.69	6
1980	N	GLY A 365	31.780	32.264	14.321	1.00	10.75	8
1981	CA	GLY A 365	31.780	32.264	14.321	1.00	10.75	8
1982	CA	GLY A 366	29.857	33.799	16.295	1.00	11.91	6
1983	CA	GLY A 366	29.857	33.799	16.295	1.00	11.91	6
1984	CA	GLY A 366	28.838	34.351	15.303	1.00	14.14	6
1985	CA	GLY A 366	27.828	33.348	15.647	1.00	17.97	6
1986	CA	GLY A 366	26.475	33.032	14.646	1.00	22.02	16
1987	CA	GLY A 366	24.526	34.590	14.752	1.00	20.41	6
1988	O	GLY A 366	30.240	35.360	12.445	1.00	12.31	8
1989	N	GLY A 367	31.249	35.740	14.417	1.00	12.74	7
1990	CA	GLY A 367	31.831	36.964	13.927	1.00	13.46	6
1991	CA	GLY A 367	31.548	38.065	14.988	1.00	14.31	6
1992	CA	GLY A 367	29.727	38.282	15.741	1.00	15.38	6
1993	CA	GLY A 367	29.727	38.282	15.741	1.00	15.38	6
1994	CA	GLY A 367	28.410	38.438	17.141	1.00	16.47	6
1995	CA	GLY A 367	29.075	38.425	14.433	1.00	16.06	6
1996	CA	GLY A 367	27.776	38.629	14.845	1.00	16.89	6
1997	CA	GLY A 367	27.431	38.644	16.196	1.00	16.89	6
1998	CA	GLY A 367	26.105	38.815	16.553	1.00	16.92	8
1999	CA	GLY A 367	33.733	35.971	13.589	1.00	13.51	6
2000	O	GLY A 367	33.733	35.971	13.589	1.00	13.51	6
2001	N	GLY A 368	34.050	35.837	13.717	1.00	13.46	7
2002	CA	GLY A 368	35.472	35.957	13.368	1.00	14.18	6
2003	C	GLY A 368	35.472	35.957	13.368	1.00	14.18	6
2004	C	GLY A 368	35.289	36.369	14.599	1.00	14.83	6
2005	CA	GLY A 368	35.746	36.992	15.528	1.00	15.20	8
2006	CA	GLY A 368	35.531	35.971	14.691	1.00	14.98	7
2007	CA	GLY A 369	39.185	35.120	16.318	1.00	12.60	6
2008	CA	GLY A 369	39.185	35.120	16.318	1.00	12.60	6
2009	CA	GLY A 369	38.175	34.186	16.966	1.00	11.76	6
2010	CA	GLY A 369	39.346	37.437	15.225	1.00	16.84	6
2011	CA	GLY A 369	39.727	37.443	14.039	1.00	16.53	8
2012	CA	GLY A 370	40.568	39.488	15.712	1.00	19.16	6
2013	CA	GLY A 370	40.568	39.488	15.712	1.00	19.16	6
2014	CA	GLY A 370	39.849	40.792	16.133	1.00	22.20	6
2015	CA	GLY A 370	38.702	41.073	15.133	1.00	26.42	6
2016	CA	GLY A 370	39.254	41.271	17.736	1.00	29.66	6
2017	CA	GLY A 370	38.326	41.239	14.244	1.00	32.10	6
2018	CA	GLY A 370	41.908	40.445	16.241	1.00	35.93	7
2019	CA	GLY A 370	41.908	40.445	16.241	1.00	35.93	7
2020	O	GLY A 370	42.638	40.436	16.526	1.00	19.70	8
2021	N	GLY A 371	42.534	38.244	16.329	1.00	20.85	7
2022	CA	GLY A 371	43.889	37.991	16.742	1.00	22.15	6
2023	CA	GLY A 371	44.417	38.443	15.581	1.00	23.36	8
2024	O	GLY A 371	44.393	38.896	14.521	1.00	23.05	6
2025	N	ASP A 372	46.095	38.223	15.877	1.00	24.83	7
2026	CA	ASP A 372	47.186	38.223	15.877	1.00	24.83	7
2027	CA	ASP A 372	48.233	39.306	15.874	1.00	31.39	6
2028	CA	ASP A 372	47.762	40.121	15.968	1.00	31.39	6
2029	CA	ASP A 372	47.762	40.121	15.968	1.00	31.39	6
2030	CA	ASP A 372	47.972	41.443	17.034	1.00	37.47	8
2031	C	ASP A 372	47.972	41.443	17.034	1.00	37.47	8
2032	O	ASP A 372	47.796	37.520	14.189	1.00	27.31	6
2033	O	ASP A 372	48.870	37.818	13.613	1.00	27.65	8
2034	CA	ASP A 373	47.162	36.353	14.166	1.00	27.64	7
2035	CA	ASP A 373	47.400	35.318	13.305	1.00	27.95	6
2036	CA	ASP A 373	47.400	35.318	13.305	1.00	27.95	6
2037	CA	ASP A 373	46.393	33.416	13.642	1.00	28.21	8
2038	O	ASP A 373	47.255	35.375	11.873	1.00	28.20	8
2039	C	ASP A 373	47.400	36.189	11.366	1.00	28.10	8
2040	CA	ASP A 374	47.780	34.393	11.137	1.00	28.61	6
2041	CA	ASP A 374	47.780	34.393	11.137	1.00	28.61	6
2042	CA	ASP A 374	47.780	34.393	11.137	1.00	28.61	6
2043	CA	ASP A 374	47.780	34.393	11.137	1.00	28.61	6
2044	CA	ASP A 374	47.780	34.393	11.137	1.00	28.61	6
2045	CA	ASP A 374	47.780	34.393	11.137	1.00	28.61	6
2046	CA	ASP A 374	47.780	34.393	11.137	1.00	28.61	6
2047	CA	ASP A 374	47.780	34.393	11.137	1.00	28.61	6
2048	CA	ASP A 374	47.780	34.393	11.137	1.00	28.61	6
2049	CA	ASP A 374	47.780	34.393	11.137	1.00	28.61	6
2050	CA	ASP A 374	47.780	34.393	11.137	1.00	28.61	6
2051	CA	ASP A 374	47.780	34.393	11.137	1.00	28.61	6
2052	CA	ASP A 374	47.780	34.393	11.137	1.00	28.61	6
2053	CA	ASP A 374	47.780	34.393	11.137	1.00	28.61	6
2054	CA	ASP A 374	47.780	34.393	11.137	1.00	28.61	6
2055	CA	ASP A 374	47.780	34.393	11.137	1.00	28.61	6
2056	CA	ASP A 374	47.780	34.393	11.137	1.00	28.61	6
2057	CA	ASP A 374	47.780	34.393	11.137	1.00	28.61	6
2058	CA	ASP A 374	47.780	34.393	11.137	1.00	28.61	6
2059	CA	ASP A 374	47.780	34.393	11.137	1.00	28.61	6
2060	CA	ASP A 374	47.780	34.393	11.137	1.00	28.61	6
2061	CA	ASP A 374	47.780	34.393	11.137	1.00	28.61	6
2062	CA	ASP A 374	47.780	34.393	11.137	1.00	28.61	6
2063	CA	ASP A 374	47.780	34.393	11.137	1.00	28.61	6
2064	CA	ASP A 374	47.780	34.393	11.137	1.00	28.61	6
2065	CA	ASP A 374	47.780	34.393	11.137	1.00	28.61	6
2066	CA	ASP A 374	47.780	34.393	11.137	1.00	28.61	6
2067	CA	ASP A 374	47.780	34.393	11.137	1.00	28.61	6
2068	CA	ASP A 374	47.780	34.393	11.137	1.00	28.61	6
2069	CA	ASP A 374	47.780	34.393	11.137	1.00	28.61	6
2070	CA	ASP A 374	47.780	34.393	11.137	1.00	28.61	6
2071	CA	ASP A 374	47.780	34.393	11.137	1.00	28.61	6
2072	CA	ASP A 374	47.780	34.393	11.137	1.00	28.61	6
2073	CA	ASP A 374	47.780	34.393	11.137	1.00	28.61	6
2074	CA	ASP A 374	47.780	34.393	11.137	1.00	28.61	6

## SUBSTITUTE SHEET (RULE 26)

AI0H	3105	0	ILE A 3177	37.793	34.301	12.173	1.00	16.90	8
AI0H	3106	0	PRO A 378	32.927	30.941	10.00	1.00	16.91	7
AI0H	3107	0	PRO B 378	32.927	30.941	10.00	1.00	16.91	7
AI0H	3108	0	PRO C 378	32.927	30.941	10.00	1.00	16.91	7
AI0H	3109	0	PRO D 378	36.637	33.810	9.695	1.00	15.87	6
AI0H	3110	0	PRO E 378	36.637	33.810	9.695	1.00	15.87	6
AI0H	3111	0	PRO F 378	36.555	33.213	8.263	1.00	15.94	6
AI0H	3112	0	PRO G 378	37.023	33.835	8.263	1.00	15.94	6
AI0H	3113	0	PRO H 378	35.214	33.860	10.247	1.00	15.56	6
AI0H	3114	0	PRO I 378	35.741	32.945	10.946	1.00	15.56	6
AI0H	3115	0	PRO J 378	35.741	32.945	10.946	1.00	15.56	6
AI0H	3116	0	PRO K 378	35.596	34.960	10.370	1.00	14.37	6
AI0H	3117	0	PRO L 378	35.596	34.960	10.370	1.00	14.37	6
AI0H	3118	0	PRO M 378	32.523	36.450	10.119	1.00	13.37	6
AI0H	3119	0	PRO N 378	32.523	36.450	10.119	1.00	13.37	6
AI0H	3120	0	PRO O 378	32.523	36.450	10.119	1.00	13.37	6
AI0H	3121	0	PRO P 378	32.523	36.450	10.119	1.00	13.37	6
AI0H	3122	0	PRO Q 378	32.523	36.450	10.119	1.00	13.37	6
AI0H	3123	0	PRO R 378	32.523	36.450	10.119	1.00	13.37	6
AI0H	3124	0	PRO S 378	32.523	36.450	10.119	1.00	13.37	6
AI0H	3125	0	PRO T 378	32.523	36.450	10.119	1.00	13.37	6
AI0H	3126	0	PRO U 378	32.523	36.450	10.119	1.00	13.37	6
AI0H	3127	0	PRO V 378	32.523	36.450	10.119	1.00	13.37	6
AI0H	3128	0	PRO W 378	32.523	36.450	10.119	1.00	13.37	6
AI0H	3129	0	PRO X 378	32.523	36.450	10.119	1.00	13.37	6
AI0H	3130	0	PRO Y 378	32.523	36.450	10.119	1.00	13.37	6
AI0H	3131	0	PRO Z 378	32.523	36.450	10.119	1.00	13.37	6
AI0H	3132	0	PRO A 385	22.960	35.427	12.453	1.00	18.27	6
AI0H	3133	0	PRO B 385	22.960	35.427	12.453	1.00	18.27	6
AI0H	3134	0	PRO C 385	22.960	35.427	12.453	1.00	18.27	6
AI0H	3135	0	PRO D 385	22.960	35.427	12.453	1.00	18.27	6
AI0H	3136	0	PRO E 385	22.960	35.427	12.453	1.00	18.27	6
AI0H	3137	0	PRO F 385	22.960	35.427	12.453	1.00	18.27	6
AI0H	3138	0	PRO G 385	22.960	35.427	12.453	1.00	18.27	6
AI0H	3139	0	PRO H 385	22.960	35.427	12.453	1.00	18.27	6
AI0H	3140	0	PRO I 385	22.960	35.427	12.453	1.00	18.27	6
AI0H	3141	0	PRO J 385	22.960	35.427	12.453	1.00	18.27	6
AI0H	3142	0	PRO K 385	22.960	35.427	12.453	1.00	18.27	6
AI0H	3143	0	PRO L 385	22.960	35.427	12.453	1.00	18.27	6
AI0H	3144	0	PRO M 385	22.960	35.427	12.453	1.00	18.27	6
AI0H	3145	0	PRO N 385	22.960	35.427	12.453	1.00	18.27	6
AI0H	3146	0	PRO O 385	22.960	35.427	12.453	1.00	18.27	6
AI0H	3147	0	PRO P 385	22.960	35.427	12.453			

## SUBSTITUTE SHEET (RULE 26)

1381	ATH	ARG A 391	18.295	24.203	18.295	1.00	6.17	6
1382	CG	ARG A 391	19.637	24.301	19.009	1.00	6.17	6
1383	CE	ARG A 391	19.415	23.982	20.476	1.00	6.39	6
1384	ATH	ARG A 391	19.411	22.752	21.057	1.00	6.41	6
1385	WHI	ARG A 391	19.671	21.719	20.264	1.00	7.01	7
1386	WHI	ARG A 391	19.671	21.719	20.264	1.00	7.01	7
1387	CE	ARG A 391	19.58	22.513	22.359	1.00	6.75	6
1388	ATH	ARG A 391	19.58	22.513	22.359	1.00	6.75	6
1389	M	ARG A 392	15.462	23.860	17.089	1.00	10.42	7
1390	ATH	ARG A 392	16.061	25.811	16.184	1.00	10.42	7
1391	ATH	ARG A 392	16.061	25.811	16.184	1.00	10.42	7
1392	CE	LYS A 392	15.137	28.036	16.253	1.00	13.27	6
1393	ATH	ARG A 392	15.137	28.036	16.253	1.00	13.27	6
1394	ATH	ARG A 392	14.76	25.388	16.797	1.00	10.42	7
1395	CE	LYS A 392	14.76	25.388	16.797	1.00	10.42	7
1396	ATH	ARG A 392	12.806	31.069	16.665	1.00	23.10	6
1397	CE	LYS A 392	12.806	31.069	16.665	1.00	23.10	6
1398	M	LYS A 392	12.806	31.069	16.665	1.00	23.10	6
1399	ATH	ARG A 392	12.536	26.046	16.200	1.00	11.94	6
1400	ATH	ARG A 392	12.536	26.046	16.200	1.00	11.94	6
1401	CE	LYS A 392	12.536	26.046	16.200	1.00	11.94	6
1402	ATH	ARG A 392	12.536	26.046	16.200	1.00	11.94	6
1403	ATH	ARG A 392	12.536	26.046	16.200	1.00	11.94	6
1404	ATH	ARG A 392	12.536	26.046	16.200	1.00	11.94	6
1405	ATH	ARG A 392	12.536	26.046	16.200	1.00	11.94	6
1406	ATH	ARG A 392	12.536	26.046	16.200	1.00	11.94	6
1407	ATH	ARG A 392	12.536	26.046	16.200	1.00	11.94	6
1408	ATH	ARG A 392	12.536	26.046	16.200	1.00	11.94	6
1409	ATH	ARG A 392	12.536	26.046	16.200	1.00	11.94	6
1410	ATH	ARG A 392	12.536	26.046	16.200	1.00	11.94	6
1411	ATH	ARG A 392	12.536	26.046	16.200	1.00	11.94	6
1412	ATH	ARG A 392	12.536	26.046	16.200	1.00	11.94	6
1413	ATH	ARG A 392	12.536	26.046	16.200	1.00	11.94	6
1414	ATH	ARG A 392	12.536	26.046	16.200	1.00	11.94	6
1415	ATH	ARG A 392	12.536	26.046	16.200	1.00	11.94	6
1416	ATH	ARG A 392	12.536	26.046	16.200	1.00	11.94	6
1417	ATH	ARG A 392	12.536	26.046	16.200	1.00	11.94	6
1418	ATH	ARG A 392	12.536	26.046	16.200	1.00	11.94	6
1419	ATH	ARG A 392	12.536	26.046	16.200	1.00	11.94	6
1420	ATH	ARG A 392	12.536	26.046	16.200	1.00	11.94	6
1421	ATH	ARG A 392	12.536	26.046	16.200	1.00	11.94	6
1422	ATH	ARG A 392	12.536	26.046	16.200	1.00	11.94	6
1423	ATH	ARG A 392	12.536	26.046	16.200	1.00	11.94	6
1424	ATH	ARG A 392	12.536	26.046	16.200	1.00	11.94	6
1425	ATH	ARG A 392	12.536	26.046	16.200	1.00	11.94	6
1426	ATH	ARG A 392	12.536	26.046	16.200	1.00	11.94	6
1427								



AT04	3393	C	GLY A 415	8,376	15,470	16,143	1,00	17,18	6	14,738	16,900	9,939	1,00	10,33	6
AT04	3394	N	ASP A 416	8,376	16,904	16,148	1,00	17,23	6	14,738	16,900	9,939	1,00	10,33	6
AT04	3395	CA	ASP A 416	7,581	16,904	17,118	1,00	18,70	7	16,337	17,764	11,895	1,00	6,31	6
AT04	3396	CA	ASP A 416	6,606	16,860	17,018	1,00	20,18	6	17,570	17,816	11,716	1,00	6,45	6
AT04	3397	CG	ASP A 416	7,228	17,531	18,307	1,00	26,49	6	16,682	19,107	12,547	1,00	8,11	6
AT04	3398	CG	ASP A 416	6,358	17,615	19,355	1,00	31,33	6	15,577	15,630	9,701	1,00	10,33	6
AT04	3399	CG	ASP A 416	6,791	18,402	20,413	1,00	35,28	6	16,449	15,658	8,706	1,00	9,69	7
AT04	3400	CG	ASP A 416	5,100	17,597	16,648	1,00	20,08	6	17,486	15,763	9,361	1,00	9,38	6
AT04	3401	C	ASP A 416	5,400	17,597	16,648	1,00	20,08	6	17,486	15,763	9,361	1,00	9,38	6
AT04	3402	C	ASP A 416	5,423	16,831	15,908	1,00	20,94	6	18,723	15,226	6,121	1,00	9,43	6
AT04	3403	N	ASP A 417	4,234	17,031	16,824	1,00	22,16	7	18,723	15,226	6,121	1,00	9,43	6
AT04	3404	CA	SER A 417	2,928	17,484	16,380	1,00	23,18	6	19,705	16,065	8,971	1,00	9,31	7
AT04	3405	CA	SER A 417	1,558	16,471	16,945	1,00	27,32	6	21,016	15,474	8,873	1,00	9,28	6
AT04	3406	CG	SER A 417	1,558	16,471	16,945	1,00	27,32	6	21,016	15,474	8,873	1,00	9,28	6
AT04	3407	C	SER A 417	2,565	18,852	16,929	1,00	23,90	6	22,035	16,435	5,062	1,00	11,00	6
AT04	3408	CG	SER A 417	1,821	19,541	16,258	1,00	23,90	6	21,989	13,294	8,823	1,00	9,20	8
AT04	3409	N	SER A 418	3,145	19,217	18,073	1,00	23,61	6	22,965	14,846	7,581	1,00	9,64	7
AT04	3410	CA	SER A 418	2,982	20,541	18,628	1,00	23,56	6	24,057	14,016	7,090	1,00	10,53	6
AT04	3411	CG	SER A 418	2,982	20,541	18,628	1,00	23,56	6	24,057	14,016	7,090	1,00	10,53	6
AT04	3412	CG	SER A 418	2,660	20,195	18,352	1,00	24,90	6	23,724	13,630	5,656	1,00	11,90	6
AT04	3413	C	SER A 418	3,968	21,525	18,023	1,00	23,17	6	23,570	15,128	5,062	1,00	13,00	6
AT04	3414	N	VAL A 419	3,995	22,714	18,503	1,00	23,96	6	22,742	12,170	3,946	1,00	12,71	6
AT04	3415	N	VAL A 419	4,894	21,195	17,094	1,00	22,44	7	25,327	14,877	7,098	1,00	10,73	6
AT04	3416	CA	VAL A 419	5,793	22,233	16,490	1,00	21,33	6	26,460	14,404	7,520	1,00	10,84	8
AT04	3417	CA	VAL A 419	7,278	22,469	16,805	1,00	19,33	6	27,758	15,045	7,515	1,00	11,63	7
AT04	3418	CG	VAL A 419	7,359	23,619	12,527	1,00	19,92	6	29,390	15,409	8,889	1,00	11,39	6
AT04	3419	CG	VAL A 419	7,559	22,527	18,315	1,00	19,37	6	29,390	15,409	8,889	1,00	11,39	6
AT04	3420	C	VAL A 419	5,477	21,951	14,988	1,00	20,67	6	28,230	12,513	6,305	1,00	10,87	6
AT04	3421	N	VAL A 420	5,911	20,939	14,404	1,00	20,45	6	28,912	15,018	11,283	1,00	8,11	6
AT04	3422	N	VAL A 420	4,616	22,803	14,400	1,00	20,01	7	28,912	15,018	11,283	1,00	8,11	6
AT04	3423	CA	ALA A 420	4,174	22,558	13,017	1,00	19,28	6	28,561	12,780	7,210	1,00	11,15	7
AT04	3424	CA	ALA A 420	3,139	23,619	12,527	1,00	19,92	6	29,390	15,409	8,889	1,00	11,90	6
AT04	3425	C	ALA A 420	4,221	23,297	12,166	1,00	18,13	6	30,085	13,558	5,993	1,00	11,90	6
AT04	3426	N	ASN A 421	5,312	21,471	11,161	1,00	17,47	7	31,412	11,728	4,125	1,00	8,42	6
AT04	3427	N	ASN A 421	6,356	21,442	10,168	1,00	16,69	6	31,412	11,728	4,125	1,00	8,42	6
AT04	3428	CA	ASN A 421	6,537	22,436	9,204	1,00	19,20	6	32,413	15,275	5,717	1,00	10,97	7
AT04	3429	CG	ASN A 421	5,242	22,917	9,984	1,00	21,79	6	32,413	15,275	5,717	1,00	10,97	7
AT04	3430	CG	ASN A 421	5,242	22,917	9,984	1,00	21,79	6	32,413	15,275	5,717	1,00	10,97	7
AT04	3431	CG	ASN A 421	5,028	23,853	7,996	1,00	22,75	6	35,390	13,452	7,993	1,00	11,96	6
AT04	3432	C	ASN A 421	7,760	20,991	10,703	1,00	15,44	6	35,390	13,452	7,993	1,00	11,96	6
AT04	3433	C	ASN A 421	8,711	20,946	9,931	1,00	15,23	8	34,941	11,410	7,231	1,00	12,11	8
AT04	3434	C	ASN A 421	7,062	20,479	11,947	1,00	14,78	7	36,676	11,784	8,551	1,00	10,98	8
AT04	3435	N	SER A 422	9,064	20,339	12,042	1,00	14,31	6	35,289	13,562	5,393	1,00	12,62	6
AT04	3436	CG	SER A 422	9,064	20,339	12,042	1,00	14,31	6	35,289	13,562	5,393	1,00	12,62	6
AT04	3437	CG	SER A 422	9,148	19,345	14,623	1,00	13,60	6	36,472	13,961	5,200	1,00	12,92	7
AT04	3438	CG	SER A 422	9,148	19,345	14,623	1,00	13,60	6	36,472	13,961	5,200	1,00	12,92	7
AT04	3439	CG	SER A 422	9,158	18,795	12,009	1,00	13,67	6	35,349	12,496	4,125	1,00	13,95	6
AT04	3440	D	GLY A 423	10,717	17,932	11,459	1,00	12,79	8	33,481	13,671	1,929	1,00	13,86	8
AT04	3441	CA	GLY A 423	10,797	18,389	12,161	1,00	12,94	7	34,509	11,820	0,999	1,00	14,34	7
AT04	3442	CA	GLY A 423	11,229	17,086	11,679	1,00	12,05	6						
AT04	3443	CG	GLY A 423	12,532	18,025	10,925	1,00	11,56	6						
AT04	3444	D	GLY A 423	12,532	18,564	10,736	1,00	11,94	7						
AT04	3445	N	LEU A 424	13,562	16,612	10,736	1,00	10,94	7						

AT0M	3569	CD	PRD A 432	11,815	5,768	11,397	1,00	16,76	6
AT0M	3570	CA	PRD A 432	10,516	5,467	11,075	1,00	17,36	6
AT0M	3571	CA	PRD A 432	9,400	5,433	10,974	1,00	17,36	6
AT0M	3572	CG	PRD A 432	8,184	5,345	11,408	1,00	17,36	6
AT0M	3573	CG	PRD A 432	13,404	8,144	9,357	1,00	15,81	6
AT0M	3574	CG	PRD A 432	13,994	8,831	10,382	1,00	15,50	6
AT0M	3575	CG	PRD A 432	12,407	8,831	8,856	1,00	16,08	6
AT0M	3576	CG	PRD A 432	11,999	10,905	7,981	1,00	16,71	6
AT0M	3577	CG	PRD A 432	11,999	10,905	7,981	1,00	16,71	6
AT0M	3578	CG	PRD A 432	10,764	11,601	7,561	1,00	17,08	6
AT0M	3579	CG	PRD A 432	13,263	11,754	8,026	1,00	15,70	6
AT0M	3580	CG	PRD A 432	10,554	10,106	10,031	1,00	17,07	6
AT0M	3581	CG	PRD A 432	10,014	11,040	10,625	1,00	16,85	6
AT0M	3582	CG	PRD A 432	8,400	8,729	10,592	1,00	18,17	6
AT0M	3583	CG	PRD A 432	8,400	8,729	10,592	1,00	18,17	6
AT0M	3584	CG	PRD A 432	7,583	8,699	9,476	1,00	18,47	6
AT0M	3585	CG	PRD A 432	7,583	8,699	9,476	1,00	18,47	6
AT0M	3586	CG	PRD A 432	6,636	7,793	9,673	1,00	19,21	6
AT0M	3587	CG	PRD A 432	5,540	7,559	8,739	1,00	19,79	6
AT0M	3588	CG	PRD A 432	5,540	7,559	8,739	1,00	19,79	6
AT0M	3589	CG	PRD A 432	3,910	5,788	6,918	1,00	24,25	6
AT0M	3590	CG	PRD A 432	3,727	4,252	7,911	1,00	40,05	6
AT0M	3591	CG	PRD A 432	3,027	3,980	6,634	1,00	44,01	6
AT0M	3592	CG	PRD A 432	1,896	3,329	3,388	1,00	46,30	6
AT0M	3593	CG	PRD A 432	1,175	2,772	7,381	1,00	47,10	6
AT0M	3594	CG	PRD A 432	1,446	3,753	5,119	1,00	46,98	6
AT0M	3595	CG	PRD A 432	3,955	9,003	7,621	1,00	19,43	6
AT0M	3596	CG	PRD A 432	4,479	9,544	9,564	1,00	19,05	6
AT0M	3597	CG	PRD A 432	3,607	10,709	9,658	1,00	18,69	6
AT0M	3598	CG	PRD A 432	3,431	11,246	11,093	1,00	21,29	6
AT0M	3599	CG	PRD A 432	4,808	11,675	11,634	1,00	23,26	6
AT0M	3600	CG	PRD A 432	5,581	10,603	12,390	1,00	24,64	6
AT0M	3601	CG	PRD A 432	4,311	11,066	12,134	1,00	24,50	6
AT0M	3602	CG	PRD A 432	4,311	11,066	12,134	1,00	24,50	6
AT0M	3603	CG	PRD A 432	4,115	11,806	8,750	1,00	18,00	6
AT0M	3604	CG	PRD A 432	3,414	12,798	8,501	1,00	17,90	6
AT0M	3605	CG	PRD A 432	5,307	11,714	8,193	1,00	17,51	6
AT0M	3606	CG	PRD A 432	5,897	12,836	7,253	1,00	16,84	6
AT0M	3607	CG	PRD A 432	7,563	10,828	7,563	1,00	16,89	6
AT0M	3608	CG	PRD A 432	6,765	16,374	9,260	1,00	13,76	6
AT0M	3609	CG	PRD A 432	8,368	12,974	9,818	1,00	15,53	6
AT0M	3610	CG	PRD A 432	5,814	12,078	5,820	1,00	16,45	6
AT0M	3611	CG	PRD A 432	4,396	12,716	4,943	1,00	16,24	6
AT0M	3612	CG	PRD A 432	5,196	10,917	5,440	1,00	16,01	6
AT0M	3613	CG	PRD A 432	4,209	9,095	4,209	1,00	15,95	6
AT0M	3614	CG	PRD A 432	4,572	11,859	3,208	1,00	15,97	6
AT0M	3615	CG	PRD A 432	3,624	11,866	3,441	1,00	15,97	6
AT0M	3616	CG	PRD A 432	5,165	11,130	2,010	1,00	15,77	6
AT0M	3617	CG	PRD A 432	4,752	11,944	4,895	1,00	15,36	6
AT0M	3618	CG	PRD A 432	5,287	13,378	4,863	1,00	15,20	6

ATOM	3605	O	GLY A 446	4.924	14.124	-0.086	1.00	15.33	8
ATOM	3606	N	GLU A 447	5.963	13.897	1.827	1.00	14.73	7
ATOM	3607	C	GLU A 447	6.387	15.280	1.807	1.00	14.28	6
ATOM	3608	C	GLU A 447	6.706	15.729	3.264	1.00	14.39	6
ATOM	3609	CO	GLU A 447	7.119	15.995	5.018	1.00	13.77	6
ATOM	3610	CD	GLU A 447	7.519	15.995	6.218	1.00	13.77	6
ATOM	3611	OE1	GLU A 447	6.875	16.135	5.959	1.00	15.55	8
ATOM	3612	OE2	GLU A 447	4.721	16.000	5.929	1.00	15.31	8
ATOM	3613	O	GLU A 447	7.644	15.680	1.041	1.00	13.72	6
ATOM	3614	O	GLU A 447	8.594	16.438	0.929	1.00	13.70	6
ATOM	3615	CA	THR A 448	7.703	16.924	6.064	1.00	13.29	6
ATOM	3616	CB	THR A 448	8.481	18.432	1.179	1.00	13.29	6
ATOM	3617	CB	THR A 448	8.481	18.432	1.179	1.00	13.29	6
ATOM	3618	OE1	THR A 448	7.898	18.972	-2.231	1.00	16.23	8
ATOM	3619	OE2	THR A 448	9.066	18.047	1.697	1.00	12.81	6
ATOM	3620	O	THR A 448	9.826	18.047	1.697	1.00	12.81	6
ATOM	3621	O	THR A 448	9.440	19.036	1.876	1.00	12.53	7
ATOM	3622	C	TRP A 449	12.011	18.040	6.100	1.00	12.53	7
ATOM	3623	CA	TRP A 449	12.331	18.788	6.100	1.00	9.67	6
ATOM	3624	CB	TRP A 449	12.564	16.992	3.035	1.00	9.67	6
ATOM	3625	CG	TRP A 449	11.619	16.660	4.133	1.00	9.31	6
ATOM	3626	CD	TRP A 449	11.959	16.118	5.402	1.00	8.65	6
ATOM	3627	OE1	TRP A 449	10.762	15.974	6.129	1.00	9.46	6
ATOM	3628	OE2	TRP A 449	10.762	15.974	6.129	1.00	9.46	6
ATOM	3629	CD1	TRP A 449	10.331	14.786	6.100	1.00	9.00	6
ATOM	3630	CD1	TRP A 449	10.331	14.786	6.100	1.00	9.00	6
ATOM	3631	OE1	TRP A 449	9.710	16.414	5.351	1.00	9.39	7
ATOM	3632	OE2	TRP A 449	10.710	15.465	7.434	1.00	9.93	6
ATOM	3633	OE2	TRP A 449	13.135	15.216	7.286	1.00	7.79	6
ATOM	3634	C	TRP A 449	11.953	15.048	7.958	1.00	8.43	6
ATOM	3635	C	TRP A 449	13.168	18.721	1.320	1.00	12.82	6
ATOM	3636	N	HIS A 450	13.727	19.837	1.779	1.00	12.56	8
ATOM	3637	CA	HIS A 450	14.852	20.452	1.044	1.00	13.34	7
ATOM	3638	CB	HIS A 450	14.269	21.682	0.331	1.00	14.42	6
ATOM	3639	CG	HIS A 450	14.886	24.101	1.061	1.00	19.94	6
ATOM	3640	CD	HIS A 450	15.225	22.455	2.378	1.00	20.15	7
ATOM	3641	OE1	HIS A 450	13.725	22.455	2.378	1.00	20.15	7
ATOM	3642	OE2	HIS A 450	14.513	24.868	2.189	1.00	20.17	6
ATOM	3643	OE2	HIS A 450	16.040	20.732	3.188	1.00	13.31	6
ATOM	3644	C	HIS A 450	15.781	20.891	3.990	1.00	13.10	8
ATOM	3645	O	HIS A 450	17.301	20.807	1.520	1.00	13.09	7
ATOM	3646	CB	ASP A 451	19.467	21.725	2.375	1.00	12.90	6
ATOM	3647	CD	ASP A 451	21.008	21.054	2.191	1.00	10.97	6
ATOM	3648	CD	ASP A 451	21.008	21.054	2.191	1.00	10.97	6
ATOM	3649	OE1	ASP A 451	20.978	21.407	3.391	1.00	9.94	6
ATOM	3650	OE2	ASP A 451	22.403	22.978	1.592	1.00	11.53	8
ATOM	3651	C	ASP A 451	18.403	22.477	2.886	1.00	13.21	6
ATOM	3652	C	ASP A 451	18.403	22.477	2.886	1.00	13.21	6
ATOM	3653	CA	ILE A 452	18.064	24.235	4.641	1.00	13.24	7
ATOM	3654	CB	ILE A 452	18.064	24.235	4.641	1.00	13.24	7
ATOM	3655	CD	ILE A 452	17.495	23.677	5.994	1.00	13.03	6
ATOM	3656	OE1	ILE A 452	18.455	23.677	5.994	1.00	11.72	6
ATOM	3657	OE2	ILE A 452	18.455	23.677	5.994	1.00	11.72	6
ATOM	3658	CD	ILE A 452	18.455	23.677	5.994	1.00	11.72	6
ATOM	3659	OE1	ILE A 452	18.455	23.677	5.994	1.00	11.72	6
ATOM	3660	OE2	ILE A 452	18.455	23.677	5.994	1.00	11.72	6
ATOM	3661	C	ILE A 452	18.455	23.677	5.994	1.00	11.72	6
ATOM	3662	C	ILE A 452	18.455	23.677	5.994	1.00	11.72	6
ATOM	3663	CA	THR A 453	21.008	24.235	4.641	1.00	13.24	7
ATOM	3664	CB	THR A 453	21.008	24.235	4.641	1.00	13.24	7
ATOM	3665	CD	THR A 453	21.008	24.235	4.641	1.00	13.24	7
ATOM	3666	OE1	THR A 453	21.008	24.235	4.641	1.00	13.24	7
ATOM	3667	OE2	THR A 453	21.008	24.235	4.641	1.00	13.24	7
ATOM	3668	N	THR A 453	21.008	24.235	4.641	1.00	13.24	7
ATOM	3669	CA	GLU A 458	17.152	15.635	-7.148	1.00	36.18	6
ATOM	3670	CB	GLU A 458	17.152	15.635	-7.148	1.00	36.18	6
ATOM	3671	CD	GLU A 458	17.152	15.635	-7.148	1.00	36.18	6
ATOM	3672	OE1	GLU A 458	17.152	15.635	-7.148	1.00	36.18	6
ATOM	3673	OE2	GLU A 458	17.152	15.635	-7.148	1.00	36.18	6
ATOM	3674	C	GLU A 458	17.152	15.635	-7.148	1.00	36.18	6
ATOM	3675	C	GLU A 458	17.152	15.635	-7.148	1.00	36.18	6
ATOM	3676	CA	GLU A 458	17.152	15.635	-7.148	1.00	36.18	6
ATOM	3677	CB	GLU A 458	17.152	15.635	-7.148	1.00	36.18	6
ATOM	3678	CD	GLU A 458	17.152	15.635	-7.148	1.00	36.18	6
ATOM	3679	OE1	GLU A 458	17.152	15.635	-7.148	1.00	36.18	6
ATOM	3680	OE2	GLU A 458	17.152	15.635	-7.148	1.00	36.18	6
ATOM	3681	C	GLU A 458	17.152	15.635	-7.148	1.00	36.18	6
ATOM	3682	C	GLU A 458	17.152	15.635	-7.148	1.00	36.18	6
ATOM	3683	CA	GLU A 458	17.152	15.635	-7.148	1.00	36.18	6
ATOM	3684	CB	GLU A 458	17.152	15.635	-7.148	1.00	36.18	6
ATOM	3685	CD	GLU A 458	17.152	15.635	-7.148	1.00	36.18	6
ATOM	3686	OE1	GLU A 458	17.152	15.635	-7.148	1.00	36.18	6
ATOM	3687	OE2	GLU A 458	17.152	15.635	-7.148	1.00	36.18	6
ATOM	3688	C	GLU A 458	17.152	15.635	-7.148	1.00	36.18	6
ATOM	3689	C	GLU A 458	17.152	15.635	-7.148	1.00	36.18	6
ATOM	3690	CA	GLU A 458	17.152	15.635	-7.148	1.00	36.18	6
ATOM	3691	CB	GLU A 458	17.152	15.635	-7.148	1.00	36.18	6
ATOM	3692	CD	GLU A 458	17.152	15.635	-7.148	1.00	36.18	6
ATOM	3693	OE1	GLU A 458	17.152	15.635	-7.148	1.00	36.18	6
ATOM	3694	OE2	GLU A 458	17.152	15.635	-7.148	1.00	36.18	6
ATOM	3695	C	GLU A 458	17.152	15.635	-7.148	1.00	36.18	6
ATOM	3696	C	GLU A 458	17.152	15.635	-7.148	1.00	36.18	6
ATOM	3697	CA	GLU A 458	17.152	15.635	-7.148	1.00	36.18	6
ATOM	3698	CB	GLU A 458	17.152	15.635	-7.148	1.00	36.18	6
ATOM	3699	CD	GLU A 458	17.152	15.635	-7.148	1.00	36.18	6
ATOM	3700	OE1	GLU A 458	17.152	15.635	-7.148	1.00	36.18	6
ATOM	3701	OE2	GLU A 458	17.152	15.635	-7.148	1.00	36.18	6
ATOM	3702	C	GLU A 458	17.152	15.635	-7.148	1.00	36.18	6
ATOM	3703	C	GLU A 458	17.152	15.635	-7.148	1.00	36.18	6
ATOM	3704	CA	GLU A 458	17.152	15.635	-7.148	1.00	36.18	6
ATOM	3705	CB	GLU A 458	17.152	15.635	-7.148	1.00	36.18	6
ATOM	3706	CD	GLU A 458	17.152	15.635	-7.148	1.00	36.18	6
ATOM	3707	OE1	GLU A 458	17.152	15.635	-7.148	1.00	36.18	6
ATOM	3708	OE2	GLU A 458	17.152	15.635	-7.148	1.00	36.18	6
ATOM	3709	C	GLU A 458	17.152	15.635	-7.148	1.00	36.18	6
ATOM	3710	C	GLU A 458	17.152	15.635	-7.148	1.00	36.18	6
ATOM	3711	CA	GLU A 458	17.152	15.635	-7.148	1.00	36.18	6
ATOM	3712	CB	GLU A 458	17.152	15.635	-7.148	1.00	36.18	6
ATOM	3713	CD	GLU A 458	17.152	15.635	-7.148	1.00	36.18	6
ATOM	3714	OE1	GLU A 458	17.152	15.635	-7.148	1.00	36.18	6
ATOM	3715	OE2	GLU A 458	17.152	15.635	-7.148	1.00	36.18	6
ATOM	3716	C	GLU A 458	17.152	15.635	-7.148	1.00	36.18	6
ATOM	3717	C	GLU A 458	17.152	15.635	-7.148	1.00	36.18	6
ATOM	3718	CA	GLU A 458	17.152	15.635	-7.148	1.00	36.18	6
ATOM	3719	CB	GLU A 458	17.152	15.635	-7.148	1.00	36.18	6
ATOM	3720	CD	GLU A 458	17.152	15.635	-7.148	1.00	36.18	6
ATOM	3721	OE1	GLU A 458	17.152	15.635	-7.148	1.00	36.18	6
ATOM	3722	OE2	GLU A 458	17.152	15.635	-7.148	1.00	36.18	6
ATOM	3723	C	GLU A 458	17.152	15.635	-7.148	1.00	36.18	6
ATOM	3724	C	GLU A 458	17.152	15.635	-7.148	1.00	36.18	6
ATOM	3725	CA	GLU A 458	17.152	15.635	-7.148	1.00	36.18	6
ATOM	3726	CB	GLU A 458	17.152	15.635	-7.148	1.00	36.18	6
ATOM	3727	CD	GLU A 458	17.152	15.635	-7.148	1.00	36.18	6
ATOM	3728	OE1	GLU A 458	17.152	15.635	-7.148	1.00	36.18	6
ATOM	3729	OE2	GLU A 458	17.152	15.635	-7.148	1.00	36.18	6
ATOM	3730	C	GLU A 458	17.152	15.635	-7.148	1.00	36.18	6
ATOM	3731	C	GLU A 458	17.152	15.635	-7.148	1.00	36.18	6
ATOM	3732	CA	GLU A 458	17.152	15.635	-7.148	1.00	36.18	6
ATOM	3733	CB	GLU A 458	17.152	15.635	-7.148	1.00	36.18	6
ATOM	3734	CD	GLU A 458	17.152	15.6				

ATM	3711	CG	PRO A 459	13.437	19.885	-6.393	1.00	18.37	6	ATM	3764	CA	TRP A 467	11.840	6.686	4.486	1.00	20.35	6
ATM	3712	CG	PRO A 459	14.504	16.723	-2.839	1.00	18.47	6	ATM	3765	CG	TRP A 467	12.339	5.313	4.107	1.00	20.44	6
ATM	3713	CG	PRO A 459	14.439	15.979	-3.780	1.00	18.48	7	ATM	3766	CG	TRP A 467	12.372	4.283	5.181	1.00	20.04	6
ATM	3714	CG	VAL A 460	14.113	16.146	-1.728	1.00	18.24	7	ATM	3767	CG	TRP A 467	13.427	3.771	5.993	1.00	19.41	6
ATM	3715	CG	VAL A 460	13.987	14.691	-1.504	1.00	18.19	6	ATM	3768	CG	TRP A 467	12.844	2.826	6.880	1.00	19.61	6
ATM	3716	CG	VAL A 460	14.908	14.168	-0.379	1.00	17.56	6	ATM	3769	CG	TRP A 467	12.921	2.831	5.991	1.00	19.58	6
ATM	3717	CG	VAL A 460	14.908	14.168	-0.379	1.00	17.56	6	ATM	3770	CG	TRP A 467	12.921	2.831	5.991	1.00	19.58	6
ATM	3718	CG	VAL A 460	14.371	14.396	-0.209	1.00	18.31	6	ATM	3771	CG	TRP A 467	11.497	2.779	6.622	1.00	19.49	6
ATM	3719	CG	VAL A 460	14.371	14.396	-0.209	1.00	18.31	6	ATM	3772	CG	TRP A 467	13.593	2.102	7.824	1.00	19.59	6
ATM	3720	CG	VAL A 460	11.892	15.157	-4.728	1.00	18.03	7	ATM	3773	CG	TRP A 467	15.552	3.268	6.997	1.00	20.04	6
ATM	3721	CG	VAL A 461	11.892	15.157	-4.728	1.00	18.03	7	ATM	3774	CG	TRP A 467	14.959	2.315	7.868	1.00	19.86	6
ATM	3722	CG	VAL A 461	10.468	13.105	-1.458	1.00	17.66	6	ATM	3775	CG	TRP A 467	12.174	7.453	3.312	1.00	20.06	6
ATM	3723	CG	VAL A 461	8.163	12.564	-2.256	1.00	16.42	6	ATM	3776	CG	TRP A 467	13.356	6.193	3.372	1.00	19.55	7
ATM	3724	CG	VAL A 461	9.629	14.023	-3.678	1.00	15.12	6	ATM	3777	CG	TRP A 467	13.356	6.193	3.372	1.00	19.55	7
ATM	3725	CG	VAL A 461	10.418	11.943	-0.456	1.00	17.45	6	ATM	3778	CG	TRP A 467	13.638	9.105	2.345	1.00	19.08	6
ATM	3726	CG	VAL A 461	11.046	10.893	-0.596	1.00	17.01	8	ATM	3779	CG	TRP A 467	15.293	8.667	2.044	1.00	18.67	6
ATM	3727	CG	VAL A 462	9.707	12.111	-0.647	1.00	17.69	7	ATM	3780	CG	TRP A 467	15.969	8.121	2.908	1.00	18.51	8
ATM	3728	CG	VAL A 462	9.707	12.111	-0.647	1.00	17.69	7	ATM	3781	CG	TRP A 467	15.761	8.896	0.848	1.00	18.42	7
ATM	3729	CG	VAL A 462	9.707	12.111	-0.647	1.00	17.69	7	ATM	3782	CG	TRP A 467	17.381	7.714	-0.771	1.00	20.35	6
ATM	3730	CG	VAL A 462	9.707	12.111	-0.647	1.00	17.69	7	ATM	3783	CG	TRP A 467	17.381	7.714	-0.771	1.00	20.35	6
ATM	3731	CG	VAL A 462	9.707	12.111	-0.647	1.00	17.69	7	ATM	3784	CG	TRP A 467	18.710	7.626	-1.293	1.00	20.59	6
ATM	3732	CG	VAL A 462	10.989	12.691	-3.597	1.00	13.00	6	ATM	3785	CG	TRP A 467	18.967	7.178	-2.729	1.00	34.28	6
ATM	3733	CG	VAL A 462	11.575	12.439	-3.642	1.00	9.27	6	ATM	3786	CG	TRP A 467	19.831	6.252	-2.904	1.00	36.09	8
ATM	3734	CG	VAL A 462	8.554	10.036	-1.716	1.00	18.95	6	ATM	3787	CG	TRP A 467	18.340	7.755	-3.681	1.00	35.52	8
ATM	3735	CG	VAL A 462	8.554	10.036	-1.716	1.00	18.95	6	ATM	3788	CG	TRP A 467	17.855	9.964	-0.424	1.00	17.57	6
ATM	3736	CG	VAL A 462	8.554	10.036	-1.716	1.00	18.95	6	ATM	3789	CG	TRP A 467	17.855	9.964	-0.424	1.00	17.57	6
ATM	3737	CG	VAL A 462	8.554	10.036	-1.716	1.00	18.95	6	ATM	3790	CG	TRP A 467	18.666	10.297	1.368	1.00	17.09	7
ATM	3738	CG	VAL A 462	8.554	10.036	-1.716	1.00	18.95	6	ATM	3791	CG	TRP A 467	19.246	11.660	1.415	1.00	16.47	6
ATM	3739	CG	VAL A 462	8.554	10.036	-1.716	1.00	18.95	6	ATM	3792	CG	TRP A 467	19.076	12.181	2.851	1.00	14.77	6
ATM	3740	CG	VAL A 462	8.554	10.036	-1.716	1.00	18.95	6	ATM	3793	CG	TRP A 467	17.686	12.126	3.451	1.00	11.90	6
ATM	3741	CG	VAL A 462	8.554	10.036	-1.716	1.00	18.95	6	ATM	3794	CG	TRP A 467	17.301	11.041	4.208	1.00	11.94	6
ATM	3742	CG	VAL A 462	8.554	10.036	-1.716	1.00	18.95	6	ATM	3795	CG	TRP A 467	16.053	11.197	2.506	1.00	10.16	6
ATM	3743	CG	VAL A 462	8.554	10.036	-1.716	1.00	18.95	6	ATM	3796	CG	TRP A 467	16.053	11.197	2.506	1.00	10.16	6
ATM	3744	CG	VAL A 462	8.554	10.036	-1.716	1.00	18.95	6	ATM	3797	CG	TRP A 467	15.562	13.155	3.871	1.00	9.27	6
ATM	3745	CG	VAL A 462	8.554	10.036	-1.716	1.00	18.95	6	ATM	3798	CG	TRP A 467	15.159	12.069	4.605	1.00	9.27	6
ATM	3746	CG	VAL A 462	8.554	10.036	-1.716	1.00	18.95	6	ATM	3799	CG	TRP A 467	20.682	11.721	0.945	1.00	16.14	6
ATM	3747	CG	VAL A 462	8.554	10.036	-1.716	1.00	18.95	6	ATM	3800	CG	TRP A 467	21.406	10.761	1.154	1.00	16.37	8
ATM	3748	CG	VAL A 462	8.554	10.036	-1.716	1.00	18.95	6	ATM	3801	CG	TRP A 467	21.142	12.807	0.363	1.00	15.78	7
ATM	3749	CG	VAL A 462	8.554	10.036	-1.716	1.00	18.95	6	ATM	3802	CG	TRP A 467	22.313	13.377	-0.146	1.00	15.69	6
ATM	3750	CG	VAL A 462	8.554	10.036	-1.716	1.00	18.95	6	ATM	3803	CG	TRP A 467	22.313	13.377	-0.146	1.00	15.69	6
ATM	3751	CG	VAL A 462	8.554	10.036	-1.716	1.00	18.95	6	ATM	3804	CG	TRP A 467	21.898	12.216	-2.515	1.00	20.58	6
ATM	3752	CG	VAL A 462	8.554	10.036	-1.716	1.00	18.95	6	ATM	3805	CG	TRP A 467	22.588	11.406	-3.372	1.00	21.49	6
ATM	3753	CG	VAL A 462	8.554	10.036	-1.716	1.00	18.95	6	ATM	3806	CG	TRP A 467	20.560	11.780	-2.567	1.00	22.05	7
ATM	3754	CG	VAL A 462	8.554	10.036	-1.716	1.00	18.95	6	ATM	3807	CG	TRP A 467	20.560	11.780	-2.567	1.00	22.05	7
ATM	3755	CG	VAL A 462	8.554	10.036	-1.716	1.00	18.95	6	ATM	3808	CG	TRP A 467	21.898	12.216	-2.515	1.00	20.58	6
ATM	3756	CG	VAL A 462	8.554	10.036	-1.716	1.00	18.95	6	ATM	3809	CG	TRP A 467	22.327	15.102	0.997	1.00	15.28	8
ATM	3757	CG	VAL A 462	8.554	10.036	-1.716	1.00	18.95	6	ATM	3810	CG	TRP A 467	24.618	13.993	0.446	1.00	15.23	7
ATM	3758	CG	VAL A 462	8.554	10.036	-1.716	1.00	18.95	6	ATM	3811	CG	TRP A 467	25.529	14.978	0.964	1.00	15.01	6
ATM	3759	CG	VAL A 462	8.554	10.036	-1.716	1.00	18.95	6	ATM	3812	CG	TRP A 467	26.385	14.698	2.271	1.00	16.48	6
ATM	3760	CG	VAL A 462	8.554	10.036	-1.716	1.00	18.95	6	ATM	3813	CG	TRP A 467	26.385	14.698	2.271	1.00	16.48	6
ATM	3761	CG	VAL A 462	8.554	10.036	-1.716	1.00	18.95	6	ATM	3814	CG	TRP A 467	26.385	14.698	2.271	1.00	16.48	6
ATM	3762	CG	VAL A 462	8.554	10.036	-1.716	1.00	18.95	6	ATM	3815	CG	TRP A 467	26.385	14.698	2.271	1.00	16.48	6
ATM	3763	CG	VAL A 462	8.554	10.036	-1.716	1.00	18.95	6	ATM	3816	CG	TRP A 467	26.385	14.698	2.271	1.00	16.48	6

ATOM	3817	O	VAL A 472	27.266	14.169	-0.462	1.00	14.29	8
ATOM	3818	H	ASH A 473	27.200	16.444	-0.001	1.00	13.78	7
ATOM	3819	H	ASH A 473	28.404	16.662	-0.001	1.00	13.30	6
ATOM	3820	C	ASH A 473	29.514	18.108	-0.139	1.00	13.44	6
ATOM	3821	C	ASH A 473	29.514	18.108	-0.139	1.00	13.44	6
ATOM	3822	O	ASH A 473	26.781	17.637	-2.883	1.00	15.07	8
ATOM	3823	H	ASH A 473	27.148	19.805	-2.094	1.00	15.52	7
ATOM	3824	C	ASH A 473	29.633	16.278	-0.486	1.00	12.99	6
ATOM	3825	O	ASH A 473	29.567	16.164	-1.139	1.00	12.88	8
ATOM	3826	H	GLY A 474	30.792	16.046	-0.723	1.00	12.57	7
ATOM	3827	H	GLY A 474	32.350	16.425	0.006	1.00	11.47	6
ATOM	3828	C	GLY A 474	32.429	16.874	0.997	1.00	11.42	6
ATOM	3829	O	GLY A 474	32.305	18.054	-0.304	1.00	11.68	6
ATOM	3830	H	GLY A 475	32.940	16.534	2.058	1.00	10.93	7
ATOM	3831	H	GLY A 475	33.425	17.392	3.139	1.00	10.37	6
ATOM	3832	C	GLY A 475	32.350	16.425	0.006	1.00	10.04	6
ATOM	3833	O	GLY A 475	31.076	17.953	3.556	1.00	9.71	7
ATOM	3834	H	SER A 476	29.967	18.862	3.748	1.00	9.25	6
ATOM	3835	CA	SER A 476	29.330	19.038	2.348	1.00	10.16	6
ATOM	3836	CG	SER A 476	28.487	20.170	2.237	1.00	11.03	8
ATOM	3837	OC	SER A 476	28.910	18.374	4.718	1.00	8.87	6
ATOM	3838	C	SER A 476	27.865	19.207	3.444	1.00	8.99	7
ATOM	3839	H	SER A 476	27.865	19.207	3.444	1.00	8.99	7
ATOM	3840	CA	VAL A 477	26.711	18.975	5.099	1.00	8.42	6
ATOM	3841	H	VAL A 477	26.705	19.802	7.028	1.00	6.94	6
ATOM	3842	CB	VAL A 477	26.953	21.281	6.811	1.00	5.00	6
ATOM	3843	CG1	VAL A 477	25.389	19.640	7.754	1.00	5.67	6
ATOM	3844	CG2	VAL A 477	25.462	19.333	4.887	1.00	8.35	6
ATOM	3845	C	VAL A 477	25.462	19.333	4.887	1.00	8.35	6
ATOM	3846	H	SER A 478	24.403	18.567	5.033	1.00	8.66	7
ATOM	3847	H	SER A 478	24.087	18.761	4.442	1.00	8.36	6
ATOM	3848	CA	SER A 478	22.792	17.840	3.254	1.00	8.85	6
ATOM	3849	CB	SER A 478	23.251	18.520	2.075	1.00	11.98	8
ATOM	3850	OC	SER A 478	22.074	18.493	5.374	1.00	8.16	6
ATOM	3851	C	SER A 478	21.114	19.486	5.720	1.00	8.17	7
ATOM	3852	H	ILE A 479	21.114	19.486	5.720	1.00	8.17	7
ATOM	3853	H	ILE A 479	20.169	19.323	6.603	1.00	8.49	6
ATOM	3854	CA	ILE A 479	20.169	20.274	7.884	1.00	8.78	6
ATOM	3855	CB	ILE A 479	18.976	19.999	8.646	1.00	6.48	6
ATOM	3856	CG2	ILE A 479	21.502	20.102	8.447	1.00	6.82	6
ATOM	3857	CG1	ILE A 479	18.689	19.536	6.031	1.00	8.23	6
ATOM	3858	C	ILE A 479	18.689	19.536	6.031	1.00	8.23	6
ATOM	3859	O	ILE A 479	16.346	20.671	5.734	1.00	8.71	8
ATOM	3860	H	THR A 480	17.989	18.447	5.791	1.00	9.32	7
ATOM	3861	H	THR A 480	16.682	18.457	5.141	1.00	10.04	6
ATOM	3862	CA	THR A 480	16.431	17.093	4.465	1.00	10.47	6
ATOM	3863	CB	THR A 480	16.431	17.093	4.465	1.00	10.47	6
ATOM	3864	CG1	THR A 480	18.230	16.201	3.055	1.00	11.51	6
ATOM	3865	CG2	THR A 480	18.230	16.201	3.055	1.00	11.51	6
ATOM	3866	CE1	THR A 480	19.531	16.102	2.880	1.00	12.53	6
ATOM	3867	CE2	THR A 480	17.088	17.304	2.001	1.00	11.63	6
ATOM	3868	CD	THR A 480	17.988	17.112	0.996	1.00	12.21	6
ATOM	3869	CE	THR A 480	19.177	16.496	1.294	1.00	12.89	6
ATOM	3870	OH	TYR A 480	38.712	30.713	38.542	1.00	7.22	8
ATOM	3871	C	TYR A 480	38.712	30.713	38.542	1.00	7.22	8
ATOM	3872	O	TYR A 480	38.712	30.713	38.542	1.00	7.22	8
ATOM	3873	CA	VAL A 481	15.497	18.052	6.064	1.00	10.40	6
ATOM	3874	CB	VAL A 481	15.497	18.052	6.064	1.00	10.40	6
ATOM	3875	CG1	VAL A 481	13.520	19.904	9.431	1.00	12.11	6
ATOM	3876	CG2	VAL A 481	13.520	19.904	9.431	1.00	12.11	6
ATOM	3877	CG3	VAL A 481	16.800	22.458	6.319	1.00	10.53	6
ATOM	3878	CG4	VAL A 481	16.800	22.458	6.319	1.00	10.53	6
ATOM	3879	C	VAL A 481	12.268	20.106	5.458	1.00	13.24	6
ATOM	3880	H	GLU A 482	12.268	20.106	5.458	1.00	13.24	6
ATOM	3881	H	GLU A 482	11.060	20.900	5.969	1.00	14.41	7
ATOM	3882	CA	GLU A 482	11.060	20.900	5.969	1.00	14.41	7
ATOM	3883	CB	GLU A 482	8.631	20.528	5.864	1.00	15.38	6
ATOM	3884	CG	GLU A 482	8.631	20.528	5.864	1.00	15.38	6
ATOM	3885	CD	GLU A 482	7.544	21.053	4.176	1.00	23.44	6
ATOM	3886	CE	GLU A 482	6.745	20.125	4.176	1.00	23.44	6
ATOM	3887	CF	GLU A 482	6.283	19.145	4.766	1.00	25.61	8
ATOM	3888	CG1	GLU A 482	6.540	20.395	2.875	1.00	25.49	7
ATOM	3889	CG2	GLU A 482	6.540	20.395	2.875	1.00	25.49	7
ATOM	3890	CG3	GLU A 482	10.406	21.644	4.755	1.00	16.28	6
ATOM	3891	CG4	GLU A 482	10.406	21.644	4.755	1.00	16.28	6
ATOM	3892	H	ARG A 483	9.856	21.490	2.934	1.00	16.75	7
ATOM	3893	CA	ARG A 483	9.955	22.625	2.026	1.00	17.07	6
ATOM	3894	CB	ARG A 483	9.913	22.081	0.609	1.00	18.13	6
ATOM	3895	CG	ARG A 483	9.621	23.031	-0.524	1.00	19.43	6
ATOM	3896	CG1	ARG A 483	10.139	23.756	-1.071	1.00	22.10	6
ATOM	3897	CG2	ARG A 483	10.139	23.756	-1.071	1.00	22.10	6
ATOM	3898	CG3	ARG A 483	11.940	25.939	-0.458	1.00	24.98	7
ATOM	3899	CG4	ARG A 483	11.940	25.939	-0.458	1.00	24.98	7
ATOM	3900	CA	ARG A 483	12.515	26.796	-1.651	1.00	26.83	7
ATOM	3901	CB	ARG A 483	12.081	26.726	0.575	1.00	27.28	7
ATOM	3902	CG	ARG A 483	8.817	23.598	2.308	1.00	17.44	6
ATOM	3903	CG1	ARG A 483	9.004	24.833	2.203	1.00	17.43	8
ATOM	3904	CG2	ARG A 483	9.004	24.833	2.203	1.00	17.43	8
ATOM	3905	CG3	ARG A 483	7.689	23.159	2.331	1.00	18.43	8
ATOM	3906	CG4	ARG A 483	7.689	23.159	2.331	1.00	18.43	8
ATOM	3907	CA	ARG A 483	43.109	24.929	31.930	1.00	10.30	20
ATOM	3908	CB	ARG A 483	43.109	24.929	31.930	1.00	10.30	20
ATOM	3909	CG	ARG A 483	36.437	9.091	7.752	1.00	19.31	20
ATOM	3910	CG1	ARG A 483	5.896	16.803	8.528	1.00	17.57	20
ATOM	3911	CG2	ARG A 483	5.896	16.803	8.528	1.00	17.57	20
ATOM	3912	CG3	ARG A 483	46.182	29.694	41.805	1.00	5.00	8
ATOM	3913	CG4	ARG A 483	39.434	45.537	34.032	1.00	7.97	8
ATOM	3914	CA	ARG A 483	31.032	40.198	39.664	1.00	5.16	8
ATOM	3915	CB	ARG A 483	31.032	40.198	39.664	1.00	5.16	8
ATOM	3916	CG	ARG A 483	34.346	20.929	31.645	1.00	5.00	8
ATOM	3917	CG1	ARG A 483	34.346	20.929	31.645	1.00	5.00	8
ATOM	3918	CG2	ARG A 483	34.507	18.918	21.861	1.00	11.20	8
ATOM	3919	CG3	ARG A 483	36.313	44.279	32.223	1.00	6.82	8
ATOM	3920	CG4	ARG A 483	39.624	39.129	42.515	1.00	5.00	8
ATOM	3921	CA	ARG A 483	30.223	47.484	41.150	1.00	8.45	8
ATOM	3922	CB	ARG A 483	30.223	47.484	41.150	1.00	8.45	8
ATOM	3923	CG	ARG A 483	39.320	27.445	41.342	1.00	6.36	8
ATOM	3924	CG1	ARG A 483	39.320	27.445	41.342	1.00	6.36	8
ATOM	3925	CG2	ARG A 483	31.724	19.710	23.165	1.00	13.82	8
ATOM	3926	CG3	ARG A 483	5.684	18.460	1.089	1.00	13.82	8
ATOM	3927	CG4	ARG A 483	38.823	36.243	42.467	1.00	5.27	8
ATOM	3928	CA	ARG A 483	31.438	41.652	35.589	1.00	5.00	8
ATOM	3929	CB	ARG A 483	31.438	41.652	35.589	1.00	5.00	8
ATOM	3930	CG	ARG A 483	38.712	30.713	38.542	1.00	7.22	8

AT0M	3923	0409	0401	X	2	42.991	28.597	56.879	1.00	19.54	8
AT0M	3924	0409	0401	X	3	42.416	31.909	17.726	1.00	10.85	8
AT0M	3925	0401	0401	X	3	48.842	22.753	4.400	1.00	10.16	8
AT0M	3926	0401	0401	X	3	48.842	22.753	4.400	1.00	10.16	8
AT0M	3927	0401	0401	X	3	58.570	25.578	42.443	1.00	10.51	8
AT0M	3928	0401	0401	X	3	35.732	43.924	49.082	1.00	5.95	8
AT0M	3929	0401	0401	X	3	26.190	18.692	1.154	1.00	10.12	8
AT0M	3930	0406	0401	X	3	40.723	25.525	46.044	1.00	10.44	8
AT0M	3931	0407	0401	X	3	41.640	28.398	45.135	1.00	5.00	8
AT0M	3932	0401	0401	X	3	40.989	21.110	52.991	1.00	10.54	8
AT0M	3933	0401	0401	X	3	26.089	27.410	12.493	1.00	10.34	8
AT0M	3934	0401	0401	X	3	22.073	12.907	32.231	1.00	10.97	8
AT0M	3935	0401	0401	X	4	22.844	23.707	36.872	1.00	9.80	8
AT0M	3936	0402	0401	X	4	36.012	18.648	48.284	1.00	17.35	8
AT0M	3937	0403	0401	X	4	31.899	45.870	33.523	1.00	10.11	8
AT0M	3938	0401	0401	X	4	22.073	12.907	32.231	1.00	10.97	8
AT0M	3939	0401	0401	X	4	40.488	14.451	42.396	1.00	12.74	8
AT0M	3940	0401	0401	X	4	53.405	37.236	44.839	1.00	12.00	8
AT0M	3941	0407	0401	X	4	43.306	20.817	52.968	1.00	25.21	8
AT0M	3942	0409	0401	X	4	45.712	34.753	17.330	1.00	22.47	8
AT0M	3943	0401	0401	X	5	10.644	19.211	8.427	1.00	8.04	8
AT0M	3944	0401	0401	X	5	23.407	21.100	30.729	1.00	15.19	8
AT0M	3945	0401	0401	X	5	34.672	39.007	47.914	1.00	20.93	8
AT0M	3946	0401	0401	X	5	39.440	24.513	6.213	1.00	25.60	8
AT0M	3947	0401	0401	X	5	43.207	54.381	40.149	1.00	25.71	8
AT0M	3948	0401	0401	X	5	79.287	22.320	29.644	1.00	17.08	8
AT0M	3949	0401	0401	X	5	42.657	37.701	31.679	1.00	16.67	8
AT0M	3950	0401	0401	X	5	43.242	40.111	24.206	1.00	19.05	8
AT0M	3951	0401	0401	X	5	27.361	18.395	39.419	1.00	14.74	8
AT0M	3952	0401	0401	X	5	26.339	52.900	35.976	1.00	18.51	8
AT0M	3953	0401	0401	X	5	22.840	21.238	35.476	1.00	13.61	8
AT0M	3954	0401	0401	X	5	38.940	13.322	9.024	1.00	11.51	8
AT0M	3955	0401	0401	X	5	25.342	16.185	20.356	1.00	18.86	8
AT0M	3956	0401	0401	X	5	8.361	17.239	9.642	1.00	13.52	8
AT0M	3957	0401	0401	X	5	37.794	6.917	7.269	1.00	20.73	8
AT0M	3958	0401	0401	X	5	36.427	41.328	48.304	1.00	11.02	8
AT0M	3959	0401	0401	X	5	41.263	35.394	49.866	1.00	22.49	8
AT0M	3960	0401	0401	X	5	25.131	39.394	49.866	1.00	10.30	8
AT0M	3961	0401	0401	X	5	51.050	21.873	54.397	1.00	18.11	8
AT0M	3962	0401	0401	X	5	43.851	50.827	56.978	1.00	18.82	8
AT0M	3963	0401	0401	X	5	27.717	49.514	27.944	1.00	19.57	8
AT0M	3964	0401	0401	X	5	32.551	52.703	28.488	1.00	9.04	8
AT0M	3965	0401	0401	X	5	44.885	26.009	54.445	1.00	7.24	8
AT0M	3966	0401	0401	X	5	38.325	36.644	45.393	1.00	19.65	8
AT0M	3967	0401	0401	X	5	21.609	12.965	20.907	1.00	9.32	8
AT0M	3968	0401	0401	X	5	13.555	13.555	25.944	1.00	9.36	8
AT0M	3969	0401	0401	X	5	42.174	43.789	25.824	1.00	28.45	8
AT0M	3970	0401	0401	X	5	42.174	43.789	25.824	1.00	28.45	8
AT0M	3971	0401	0401	X	5	42.174	43.789	25.824	1.00	28.45	8
AT0M	3972	0401	0401	X	5	42.174	43.789	25.824	1.00	28.45	8
AT0M	3973	0401	0401	X	5	42.174	43.789	25.824	1.00	28.45	8
AT0M	3974	0401	0401	X	5	42.174	43.789	25.824	1.00	28.45	8
AT0M	3975	0401	0401	X	5	42.174	43.789	25.824	1.00	28.45	8
AT0M	3976	0401	0401	X	5	42.174	43.789	25.824	1.00	28.45	8
AT0M	3977	0401	0401	X	5	42.174	43.789	25.824	1.00	28.45	8
AT0M	3978	0401	0401	X	5	42.174	43.789	25.824	1.00	28.45	8
AT0M	3979	0401	0401	X	5	42.174	43.789	25.824	1.00	28.45	8
AT0M	3980	0401	0401	X	5	42.174	43.789	25.824	1.00	28.45	8
AT0M	3981	0401	0401	X	5	42.174	43.789	25.824	1.00	28.45	8
AT0M	3982	0401	0401	X	5	42.174	43.789	25.824	1.00	28.45	8
AT0M	3983	0401	0401	X	5	42.174	43.789	25.824	1.00	28.45	8
AT0M	3984	0401	0401	X	5	42.174	43.789	25.824	1.00	28.45	8
AT0M	3985	0401	0401	X	5	42.174	43.789	25.824	1.00	28.45	8
AT0M	3986	0401	0401	X	5	42.174	43.789	25.824	1.00	28.45	8
AT0M	3987	0401	0401	X	5	42.174	43.789	25.824	1.00	28.45	8
AT0M	3988	0401	0401	X	5	42.174	43.789	25.824	1.00	28.45	8
AT0M	3989	0401	0401	X	5	42.174	43.789	25.824	1.00	28.45	8
AT0M	3990	0401	0401	X	5	42.174	43.789	25.824	1.00	28.45	8
AT0M	3991	0401	0401	X	5	42.174	43.789	25.824	1.00	28.45	8
AT0M	3992	0401	0401	X	5	42.174	43.789	25.824	1.00	28.45	8
AT0M	3993	0401	0401	X	5	42.174	43.789	25.824	1.00	28.45	8
AT0M	3994	0401	0401	X	5	42.174	43.789	25.824	1.00	28.45	8
AT0M	3995	0401	0401	X	5	42.174	43.789	25.824	1.00	28.45	8
AT0M	3996	0401	0401	X	5	42.174	43.789	25.824	1.00	28.45	8
AT0M	3997	0401	0401	X	5	42.174	43.789	25.824	1.00	28.45	8
AT0M	3998	0401	0401	X	5	42.174	43.789	25.824	1.00	28.45	8
AT0M	3999	0401	0401	X	5	42.174	43.789	25.824	1.00	28.45	8
AT0M	4000	0401	0401	X	5	42.174	43.789	25.824	1.00	28.45	8
AT0M	4001	0401	0401	X	5	42.174	43.789	25.824	1.00	28.45	8
AT0M	4002	0401	0401	X	5	42.174	43.789	25.824	1.00	28.45	8
AT0M	4003	0401	0401	X	5	42.174	43.789	25.824	1.00	28.45	8
AT0M	4004	0401	0401	X	5	42.174	43.789	25.824	1.00	28.45	8
AT0M	4005	0401	0401	X	5	42.174	43.789	25.824	1.00	28.45	8
AT0M	4006	0401	0401	X	5	42.174	43.789	25.824	1.00	28.45	8
AT0M	4007	0401	0401	X	5	42.174	43.789	25.824	1.00	28.45	8
AT0M	4008	0401	0401	X	5	42.174	43.789	25.824	1.00	28.45	8
AT0M	4009	0401	0401	X	5	42.174	43.789	25.824	1.00	28.45	8
AT0M	4010	0401	0401	X	5	42.174	43.789	25.824	1.00	28.45	8
AT0M	4011	0401	0401	X	5	42.174	43.789	25.824	1.00	28.45	8
AT0M	4012	0401	0401	X	5	42.174	43.789	25.824	1.00	28.45	8
AT0M	4013	0401	0401	X	5	42.174	43.789	25.824	1.00	28.45	8
AT0M	4014	0401	0401	X	5	42.174	43.789	25.824	1.00	28.45	8
AT0M	4015	0401	0401	X	5	42.174	43.789	25.824	1.00	28.45	8
AT0M	4016	0401	0401	X	5	42.174	43.789	25.824	1.00	28.45	8
AT0M	4017	0401	0401	X	5	42.174	43.789	25.824	1.00	28.45	8
AT0M	4018	0401	0401	X	5	42.174	43.789	25.824	1.00	28.45	8
AT0M	4019	0401	0401	X	5	42.174	43.789	25.824	1.00	28.45	8
AT0M	4020	0401	0401	X	5	42.174	43.789	25.824	1.00	28.45	8
AT0M	4021	0401	0401	X	5	42.174	43.789	25.824	1.00	28.45	8
AT0M	4022	0401	0401	X	5	42.174	43.789	25.824	1.00	28.45	8
AT0M	4023	0401	0401	X	5	42.174	43.789	25.824	1.00	28.45	8
AT0M	4024	0401	0401	X	5	42.174	43.789	25.824	1.00	28.45	8
AT0M	4025	0401	0401	X	5	42.174	43.789	25.824	1.00	28.45	8
AT0M	4026	0401	0401	X	5	42.174	43.789	25.824	1.00	28.45	8
AT0M	4027	0401	0401	X	5	42.174	43.789	25.824	1.00	28.45	8
AT0M	4028	0401	0401	X	5	42.174	43.789	25.824	1.00	28.45	8

AT04	4039	0405	0407	0408	0409	0410	0411	0412	0413	0414	0415	0416	0417	0418	0419	0420	0421	0422	0423	0424	0425	0426	0427	0428	0429	0430	0431	0432	0433	0434	0435	0436	0437	0438	0439	0440	0441	0442	0443	0444	0445	0446	0447	0448	0449	0450	0451	0452	0453	0454	0455	0456	0457	0458	0459	0460	0461	0462	0463	0464	0465	0466	0467	0468	0469	0470	0471	0472	0473	0474	0475	0476	0477	0478	0479	0480	0481	0482	0483	0484	0485	0486	0487	0488	0489	0490	0491	0492	0493	0494	0495	0496	0497	0498	0499	0500	0501	0502	0503	0504	0505	0506	0507	0508	0509	0510	0511	0512	0513	0514	0515	0516	0517	0518	0519	0520	0521	0522	0523	0524	0525	0526	0527	0528	0529	0530	0531	0532	0533	0534	0535	0536	0537	0538	0539	0540	0541	0542	0543	0544	0545	0546	0547	0548	0549	0550	0551	0552	0553	0554	0555	0556	0557	0558	0559	0560	0561	0562	0563	0564	0565	0566	0567	0568	0569	0570	0571	0572	0573	0574	0575	0576	0577	0578	0579	0580	0581	0582	0583	0584	0585	0586	0587	0588	0589	0590	0591	0592	0593	0594	0595	0596	0597	0598	0599	0600	0601	0602	0603	0604	0605	0606	0607	0608	0609	0610	0611	0612	0613	0614	0615	0616	0617	0618	0619	0620	0621	0622	0623	0624	0625	0626	0627	0628	0629	0630	0631	0632	0633	0634	0635	0636	0637	0638	0639	0640	0641	0642	0643	0644	0645	0646	0647	0648	0649	0650	0651	0652	0653	0654	0655	0656	0657	0658	0659	0660	0661	0662	0663	0664	0665	0666	0667	0668	0669	0670	0671	0672	0673	0674	0675	0676	0677	0678	0679	0680	0681	0682	0683	0684	0685	0686	0687	0688	0689	0690	0691	0692	0693	0694	0695	0696	0697	0698	0699	0700	0701	0702	0703	0704	0705	0706	0707	0708	0709	0710	0711	0712	0713	0714	0715	0716	0717	0718	0719	0720	0721	0722	0723	0724	0725	0726	0727	0728	0729	0730	0731	0732	0733	0734	0735	0736	0737	0738	0739	0740	0741	0742	0743	0744	0745	0746	0747	0748	0749	0750	0751	0752	0753	0754	0755	0756	0757	0758	0759	0760	0761	0762	0763	0764	0765	0766	0767	0768	0769	0770	0771	0772	0773	0774	0775	0776	0777	0778	0779	0780	0781	0782	0783	0784	0785	0786	0787	0788	0789	0790	0791	0792	0793	0794	0795	0796	0797	0798	0799	0800	0801	0802	0803	0804	0805	0806	0807	0808	0809	0810	0811	0812	0813	0814	0815	0816	0817	0818	0819	0820	0821	0822	0823	0824	0825	0826	0827	0828	0829	0830	0831	0832	0833	0834	0835	0836	0837	0838	0839	0840	0841	0842	0843	0844	0845	0846	0847	0848	0849	0850	0851	0852	0853	0854	0855	0856	0857	0858	0859	0860	0861	0862	0863	0864	0865	0866	0867	0868	0869	0870	0871	0872	0873	0874	0875	0876	0877	0878	0879	0880	0881	0882	0883	0884	0885	0886	0887	0888	0889	0890	0891	0892	0893	0894	0895	0896	0897	0898	0899	0900	0901	0902	0903	0904	0905	0906	0907	0908	0909	0910	0911	0912	0913	0914	0915	0916	0917	0918	0919	0920	0921	0922	0923	0924	0925	0926	0927	0928	0929	0930	0931	0932	0933	0934	0935	0936	0937	0938	0939	0940	0941	0942	0943	0944	0945	0946	0947	0948	0949	0950	0951	0952	0953	0954	0955	0956	0957	0958	0959	0960	0961	0962	0963	0964	0965	0966	0967	0968	0969	0970	0971	0972	0973	0974	0975	0976	0977	0978	0979	0980	0981	0982	0983	0984	0985	0986	0987	0988	0989	0990	0991	0992	0993	0994	0995	0996	0997	0998	0999	1000	1001	1002	1003	1004	1005	1006	1007	1008	1009	1010	1011	1012	1013	1014	1015	1016	1017	1018	1019	1020	1021	1022	1023	1024	1025	1026	1027	1028	1029	1030	1031	1032	1033	1034	1035	1036	1037	1038	1039	1040	1041	1042	1043	1044	1045	1046	1047	1048	1049	1050	1051	1052	1053	1054	1055	1056	1057	1058	1059	1060	1061	1062	1063	1064	1065	1066	1067	1068	1069	1070	1071	1072	1073	1074	1075	1076	1077	1078	1079	1080	1081	1082	1083	1084	1085	1086	1087	1088	1089	1090	1091	1092	1093	1094	1095	1096	1097	1098	1099	1100	1101	1102	1103	1104	1105	1106	1107	1108	1109	1110	1111	1112	1113	1114	1115	1116	1117	1118	1119	1120	1121	1122	1123	1124	1125	1126	1127	1128	1129	1130	1131	1132	1133	1134	1135	1136	1137	1138	1139	1140	1141	1142	1143	1144	1145	1146	1147	1148	1149	1150	1151	1152	1153	1154	1155	1156	1157	1158	1159	1160	1161	1162	1163	1164	1165	1166	1167	1168	1169	1170	1171	1172	1173	1174	1175	1176	1177	1178	1179	1180	1181	1182	1183	1184	1185	1186	1187	1188	1189	1190	1191	1192	1193	1194	1195	1196	1197	1198	1199	1200	1201	1202	1203	1204	1205	1206	1207	1208	1209	1210	1211	1212	1213	1214	1215	1216	1217	1218	1219	1220	1221	1222	1223	1224	1225	1226	1227	1228	1229	1230	1231	1232	1233	1234	1235	1236	1237	1238	1239	1240	1241	1242	1243	1244	1245	1246	1247	1248	1249	1250	1251	1252	1253	1254	1255	1256	1257	1258	1259	1260	1261	1262	1263	1264	1265	1266	1267	1268	1269	1270	1271	1272	1273	1274	1275	1276	1277	1278	1279	1280	1281	1282	1283	1284	1285	1286	1287	1288	1289	1290	1291	1292	1293	1294	1295	1296	1297	1298	1299	1300	1301	1302	1303	1304	1305	1306	1307	1308	1309	1310	1311	1312	1313	1314	1315	1316	1317	1318	1319	1320	1321	1322	1323	1324	1325	1326	1327	1328	1329	1330	1331	1332	1333	1334	1335	1336	1337	1338	1339	1340	1341	1342	1343	1344	1345	1346	1347	1348	1349	1350	1351	1352	1353	1354	1355	1356	1357	1358	1359	1360	1361	1362	1363	1364	1365	1366	1367	1368	1369	1370	1371	1372	1373	1374	1375	1376	1377	1378	1379	1380	1381	1382	1383	1384	1385	1386	1387	1388	1389	1390	1391	1392	1393	1394	1395	1396	1397	1398	1399	1400	1401	1402	1403	1404	1405	1406	1407	1408	1409	1410	1411	1412	1413	1414	1415	1416	1417	1418	1419	1420	1421	1422	1423	1424	1425	1426	1427	1428	1429	1430	1431	1432	1433	1434	1435	1436	1437	1438	1439	1440	1441	1442	1443	1444	1445	1446	1447	1448	1449	1450	1451	1452	1453	1454	1455	1456	1457	1458	1459	1460	1461	1462	1463	1464	1465	1466	1467	1468	1469	1470	1471	1472	1473	1474	1475	1476	1477	1478	1479	1480	1481	1482	1483	1484	1485	1486	1487	1488	1489	1490	1491	1492	1493	1494	1495	1496	1497	1498	1499	1500	1501	1502	1503	1504	1505	1506	1507	1508	1509	1510	1511	1512	1513	1514	1515	1516	1517	1518	1519	1520	1521	1522	1523	1524	1525	1526	1527	1528	1529	1530	1531	1532	1533	1534	1535	1536	1537	1538	1539	1540	1541	1542	1543	1544	1545	1546	1547	1548	1549	1550	1551	1552	1553	1554	1555	1556	1557	1558	1559	1560	1561	1562	1563	1564	1565	1566	1567	1568	1569	1570	1571	1572	1573	1574	1575	1576	1577	1578	1579	1580	1581	1582	1583	1584	1585	1586	1587	1588	1589	1590	1591	1592	1593	1594	1595	1596	1597	1598	1599	1600	1601	1602	1603	1604	1605	1606	1607	1608	1609	1610	1611	1612	1613	1614	1615	1616	1617	1618	1619	1620	1621	1622	1623	1624	1625	1626	1627	1628	1629	1630	1631	1632	1633	1634	1635	1636	1637	1638	1639	1640	1641	1642	1643	1644	1645	1646	1647	1648	1649	1650	1651	1652	1653	1654	1655	1656	1657	1658	1659	1660	1661	1662	1663	1664	1665	1666	1667	1668	1669	1670	1671	1672	1673	1674	1675	1676	1677	1678	1679	1680	1681	1682	1683	1684	1685	1686	1687	1688	1689	1690	1691	1692	1693	1694	1695	1696	1697	1698	1699	1700	1701	1702	1703	1704	1705	1706	1707	1708	1709	1710	1711	1712	1713	1714	1715	1716	1717	1718	1719	1720	1721	1722	1723	1724	1725	1726	1727	1728	1729	1730	1731	1732	1733	1734	1735	1736	1737	1738	1739	1740	1741	1742	1743	1744	1745	1746	1747	1748	1749	1750	1751	1752	1753	1754	1755	1756	1757	1758	1759	1760	1761	1762	1763</
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AT04	4135	041	041	X	24	26.342	44.862	18.030	1.00	27.39	8
AT04	4136	042	041	X	24	42.233	42.957	42.250	1.00	44.47	8
AT04	4137	043	041	X	24	42.957	42.957	42.250	1.00	44.47	8
AT04	4138	045	041	X	24	18.776	45.302	34.694	1.00	36.85	8
AT04	4139	045	041	X	24	17.379	48.302	34.694	1.00	36.85	8
AT04	4140	047	041	X	24	59.859	17.628	38.947	1.00	24.00	8
AT04	4141	047	041	X	24	44.716	26.865	15.361	1.00	31.66	8
AT04	4142	040	041	X	24	16.851	22.367	25.144	1.00	38.33	8
AT04	4143	040	041	X	24	51.826	36.690	57.769	1.00	27.31	8
AT04	4144	041	041	X	25	51.826	36.690	57.769	1.00	27.31	8
AT04	4145	041	041	X	25	63.688	40.328	57.339	1.00	34.91	8
AT04	4146	042	041	X	25	43.373	15.118	12.332	1.00	38.80	8
AT04	4147	043	041	X	25	29.409	35.711	7.381	1.00	30.09	8
AT04	4148	044	041	X	25	26.515	13.237	-3.713	1.00	30.32	8
AT04	4149	045	041	X	25	30.572	42.011	16.433	1.00	30.32	8
AT04	4150	046	041	X	25	52.071	42.011	16.433	1.00	30.32	8
AT04	4151	047	041	X	25	41.643	52.238	24.422	1.00	33.83	8
AT04	4152	049	041	X	25	18.346	37.047	42.302	1.00	35.93	8
AT04	4153	049	041	X	25	35.262	56.671	32.779	1.00	56.94	8
AT04	4154	040	041	X	26	44.229	16.673	16.585	1.00	37.25	8
AT04	4155	041	041	X	26	11.356	31.920	59.134	1.00	33.03	8
AT04	4156	041	041	X	26	12.971	21.397	23.449	1.00	37.99	8
AT04	4157	043	041	X	26	41.259	51.310	51.509	1.00	40.81	8
AT04	4158	044	041	X	26	41.929	11.622	42.697	1.00	45.17	8
AT04	4159	046	041	X	26	42.707	43.759	57.270	1.00	42.42	8
AT04	4160	046	041	X	26	29.216	2.107	37.807	1.00	35.01	8
AT04	4161	047	041	X	26	36.421	11.342	-3.728	1.00	33.27	8
AT04	4162	047	041	X	26	40.493	39.175	53.713	1.00	47.98	8
AT04	4163	049	041	X	26	45.625	38.306	11.910	1.00	37.58	8
AT04	4164	041	041	X	27	43.801	49.874	24.898	1.00	75.20	8
AT04	4165	042	041	X	27	11.684	17.068	21.179	1.00	34.01	8
AT04	4166	043	041	X	27	29.216	2.107	37.807	1.00	35.01	8
AT04	4167	043	041	X	27	36.421	11.342	-3.728	1.00	33.27	8
AT04	4168	044	041	X	27	55.458	34.451	38.180	1.00	47.45	8
AT04	4169	046	041	X	27	49.008	19.947	34.189	1.00	43.45	8
AT04	4170	046	041	X	27	45.625	38.306	11.910	1.00	37.58	8
AT04	4171	047	041	X	27	1.742	6.632	1.900	1.00	62.88	8
AT04	4172	048	041	X	27	48.275	39.555	43.586	1.00	28.38	8
AT04	4173	049	041	X	27	23.075	42.929	53.043	1.00	51.62	8
AT04	4174	049	041	X	27	23.075	42.929	53.043	1.00	51.62	8
AT04	4175	041	041	X	28	21.533	51.619	35.565	1.00	49.86	8
AT04	4176	042	041	X	28	1.544	11.851	5.024	1.00	49.29	8
AT04	4177	043	041	X	28	22.566	43.229	55.525	1.00	28.33	8
AT04	4178	044	041	X	28	44.851	57.241	34.859	1.00	42.49	8
AT04	4179	045	041	X	28	37.186	9.184	-0.021	1.00	44.35	8
AT04	4180	046	041	X	28	37.186	9.184	-0.021	1.00	44.35	8
AT04	4181	047	041	X	28	56.162	41.254	59.120	1.00	56.59	8
AT04	4182	048	041	X	28	5.756	19.201	7.132	1.00	20.05	8
AT04	4183	049	041	X	28	14.700	29.886	48.605	1.00	35.67	8
AT04	4184	040	041	X	29	41.585	56.275	32.373	1.00	42.13	8
AT04	4185	041	041	X	29	26.084	9.694	43.922	1.00	49.12	8
AT04	4186	042	041	X	29	26.084	9.694	43.922	1.00	49.12	8
AT04	4187	043	041	X	29	18.885	11.752	26.566	1.00	49.31	8
AT04	4188	044	041	X	29	18.885	11.752	26.566	1.00	49.31	8
AT04	4189	045	041	X	29	20.518	10.712	22.033	1.00	31.01	8
AT04	4190	046	041	X	29	28.355	10.712	22.033	1.00	31.01	8
AT04	4191	047	041	X	29	51.144	33.741	38.200	1.00	44.30	8
AT04	4192	048	041	X	29	50.909	32.684	61.158	1.00	44.30	8
AT04	4193	049	041	X	29	45.397	9.987	33.816	1.00	41.23	8
AT04	4194	040	041	X	30	61.383	22.553	32.910	1.00	43.24	8
AT04	4195	041	041	X	30	61.383	22.553	32.910	1.00	43.24	8
AT04	4196	042	041	X	30	35.294	56.821	39.452	1.00	34.28	8
AT04	4197	043	041	X	30	34.193	44.616	18.067	1.00	42.78	8
AT04	4198	044	041	X	30	31.695	52.889	53.190	1.00	54.83	8
AT04	4199	045	041	X	30	13.657	44.210	31.115	1.00	42.94	8
AT04	4200	046	041	X	30	17.493	40.435	33.227	1.00	42.80	8
AT04	4201	047	041	X	30	17.493	40.435	33.227	1.00	42.80	8
AT04	4202	048	041	X	30	57.671	31.407	58.700	1.00	47.82	8
AT04	4203	049	041	X	30	6.539	26.132	10.421	1.00	56.80	8
AT04	4204	040	041	X	31	49.681	16.792	34.456	1.00	56.81	8
AT04	4205	041	041	X	31	7.284	4.777	13.925	1.00	41.62	8
AT04	4206	042	041	X	31	19.862	44.869	37.796	1.00	35.48	8
AT04	4207	043	041	X	31	16.862	44.869	37.796	1.00	35.48	8
AT04	4208	044	041	X	31	40.080	55.747	29.931	1.00	44.41	8
AT04	4209	045	041	X	31	4.298	25.064	15.031	1.00	55.22	8
AT04	4210	046	041	X	31	49.649	40.424	40.847	1.00	31.66	8
AT04	4211	047	041	X	31	22.128	29.127	52.419	1.00	40.80	8
AT04	4212	048	041	X	31	19.283	33.605	36.184	1.00	38.09	8
AT04	4213	049	041	X	31	16.931	37.437	36.501	1.00	33.72	8
AT04	4214	040	041	X	32	16.931	37.437	36.501	1.00	33.72	8
AT04	4215	041	041	X	32	7.050	10.365	16.890	1.00	37.40	8
AT04	4216	042	041	X	32	50.382	29.410	35.312	1.00	56.52	8
AT04	4217	043	041	X	32	27.086	47.626	17.616	1.00	31.50	8
AT04	4218	044	041	X	32	50.029	47.626	17.616	1.00	31.50	8
AT04	4219	045	041	X	32	29.154	55.495	24.292	1.00	53.90	8
AT04	4220	046	041	X	32	29.170	48.486	34.932	1.00	46.52	8
AT04	4221	047	041	X	32	25.242	20.725	9.284	1.00	45.90	8
AT04	4222	048	041	X	32	41.947	30.725	9.284	1.00	45.90	8
AT04	4223	049	041	X	32	21.381	14.261	36.815	1.00	44.69	8
AT04	4224	040	041	X	33	60.941	22.089	43.042	1.00	37.06	8
AT04	4225	041	041	X	33	40.505	56.155	62.947	1.00	68.99	8
AT04	4226	042	041	X	33	18.578	37.434	47.553	1.00	35.06	8
AT04	4227	043	041	X	33	20.611	21.237	38.432	1.00	42.40	8
AT04	4228	044	041	X	33	20.611	21.237	38.432	1.00	42.40	8
AT04	4229	045	041	X	33	38.037	3.708	21.690	1.00	53.54	8
AT04	4230	046	041	X	33	18.925	37.694	11.766	1.00	57.07	8
AT04	4231	047	041	X	33	53.097	28.032	37.987	1.00	57.12	8
AT04	4232	048	041	X	33	61.148	18.349	37.733	1.00	40.38	8
AT04	4233	049	041	X	33	22.608	32.712	41.553	1.00	37.92	8
AT04	4234	040	041	X	34	29.443	3.779	16.367	1.00	46.74	8
AT04	4235	041	041	X	34	22.608	32.712	41.553	1.00	37.92	8
AT04	4236	042	041	X	34	41.862	17.565	7.880	1.00	10.16	8
AT04	4237	043	041	X	34	44.558	18.412	8.333	1.00	38.61	8
AT04	4238	044	041	X	34	51.913	26.059	58.542	1.00	43.05	8
AT04	4239	045	041	X	34	41.063	33.656	56.544	1.00	55.33	8
AT04	4240	046	041	X	34	34.680	53.702	32.276	1.00	47.20	8

ATOM	4241	0408	0401	WAT	34	39.667	54.253	16.713	12.011	0	100.49.12	8
ATOM	4242	0408	0401	WAT	35	39.667	54.253	16.713	12.011	0	100.49.12	8
ATOM	4243	0408	0401	WAT	36	18.706	24.337	40.234	10.51.89	0	100.51.89	8
ATOM	4244	0401	WAT	35	20.209	21.570	34.426	10.00.34.23	0	100.51.89	8	
ATOM	4245	0402	WAT	35	61.584	32.246	26.801	10.00.35.48	0	100.35.48	8	
ATOM	4246	0403	WAT	35	61.438	32.246	57.799	10.00.35.48	0	100.35.48	8	
ATOM	4247	0404	WAT	35	13.266	6.166	0.033	100.49.60	0	100.49.60	8	
ATOM	4248	0405	WAT	35	55.515	55.527	100.54.43	0	100.54.43	8		
ATOM	4249	0406	WAT	35	55.506	51.315	55.527	100.54.43	0	100.54.43	8	
ATOM	4250	0407	WAT	35	1.397	8.422	6.873	100.48.48	0	100.48.48	8	
ATOM	4251	0408	WAT	35	47.778	11.907	36.953	10.00.34.48	0	100.34.48	8	
ATOM	4252	0409	WAT	35	15.856	27.767	43.003	10.00.55.40	0	100.55.40	8	
ATOM	4253	0409	WAT	36	38.734	7.626	16.829	10.00.43.46	0	100.43.46	8	
ATOM	4254	0401	WAT	36	38.734	7.626	16.829	10.00.43.46	0	100.43.46	8	
ATOM	4255	0401	WAT	36	44.622	1.626	8.281	100.49.12	0	100.49.12	8	
ATOM	4256	0401	WAT	36	44.622	1.626	8.281	100.49.12	0	100.49.12	8	
ATOM	4256	0405	WAT	36	44.622	34.879	33.356	100.60.84	0	100.60.84	8	
ATOM	4257	0404	WAT	36	1.0316	16.327	16.327	100.60.84	0	100.60.84	8	
ATOM	4258	0405	WAT	36	3.4131	56.503	45.767	100.56.22	0	100.56.22	8	
ATOM	4259	0406	WAT	36	49.548	26.337	22.216	100.53.09	0	100.53.09	8	
ATOM	4260	0407	WAT	36	37.549	29.316	4.956	100.52.92	0	100.52.92	8	
ATOM	4261	0408	WAT	36	37.549	29.316	4.956	100.52.92	0	100.52.92	8	
ATOM	4262	0409	WAT	36	55.734	15.534	14.534	100.51.96	0	100.51.96	8	
ATOM	4263	0409	WAT	37	39.061	11.166	25.498	100.34.59	0	100.34.59	8	
ATOM	4264	0401	WAT	37	10.532	4.916	16.271	100.58.74	0	100.58.74	8	
ATOM	4265	0402	WAT	37	41.316	7.373	32.768	100.47.04	0	100.47.04	8	
ATOM	4266	0403	WAT	37	32.474	4.914	15.464	100.44.27	0	100.44.27	8	
ATOM	4267	0404	WAT	37	38.592	28.534	17.068	100.41.36	0	100.41.36	8	
ATOM	4268	0405	WAT	37	38.592	28.534	17.068	100.41.36	0	100.41.36	8	
ATOM	4269	0406	WAT	37	37.567	25.537	19.003	100.45.33	0	100.45.33	8	
ATOM	4270	0407	WAT	37	37.567	57.053	47.412	100.49.88	0	100.49.88	8	
ATOM	4271	0408	WAT	37	49.434	37.594	42.185	100.39.96	0	100.39.96	8	
ATOM	4272	0409	WAT	37	42.690	28.862	30.545	100.42.38	0	100.42.38	8	
ATOM	4273	0401	WAT	38	29.822	6.331	24.708	100.48.41	0	100.48.41	8	
ATOM	4274	0402	WAT	38	43.689	32.981	31.239	100.43.26	0	100.43.26	8	
ATOM	4275	0403	WAT	38	38.715	7.492	30.920	100.52.61	0	100.52.61	8	
ATOM	4276	0404	WAT	38	46.051	16.381	10.005	100.42.77	0	100.42.77	8	
ATOM	4277	0405	WAT	38	26.231	44.941	30.291	100.58.57	0	100.58.57	8	
ATOM	4278	0406	WAT	38	41.500	26.375	9.990	100.50.76	0	100.50.76	8	
ATOM	4279	0407	WAT	38	51.550	42.087	41.209	100.45.03	0	100.45.03	8	
ATOM	4280	0408	WAT	38	38.715	7.492	30.920	100.52.61	0	100.52.61	8	
ATOM	4281	0409	WAT	38	46.051	16.381	10.005	100.42.77	0	100.42.77	8	
ATOM	4282	0401	WAT	39	26.231	44.941	30.291	100.58.57	0	100.58.57	8	
ATOM	4283	0402	WAT	39	35.909	18.255	11.310	100.53.37	0	100.53.37	8	
ATOM	4284	0403	WAT	39	43.924	10.373	31.316	100.40.13	0	100.40.13	8	
ATOM	4285	0404	WAT	39	22.933	10.397	39.495	100.42.79	0	100.42.79	8	
ATOM	4286	0405	WAT	39	19.314	48.996	21.847	100.68.43	0	100.68.43	8	
ATOM	4287	0406	WAT	39	45.455	25.565	10.005	100.60.89	0	100.60.89	8	
ATOM	4288	0407	WAT	39	45.455	25.565	10.005	100.60.89	0	100.60.89	8	
ATOM	4289	0408	WAT	39	44.078	13.029	36.066	100.37.57	0	100.37.57	8	
ATOM	4290	0409	WAT	39	27.240	0.087	12.289	100.48.13	0	100.48.13	8	
ATOM	4291	0401	WAT	39	15.804	17.374	23.200	100.45.09	0	100.45.09	8	
ATOM	4292	0402	WAT	40	23.294	12.036	34.534	100.58.48	0	100.58.48	8	
ATOM	4293	0403	WAT	40	47.490	44.003	18.005	100.60.75	0	100.60.75	8	

[illegible]



AT04	4559	043	041	X	70	12.169	0.500	-0.175	1.00100,00	8
AT04	4560	043	041	X	70	24.781	48.147	16.489	1.0033,74	8
AT04	4561	043	041	X	70	45.295	18.629	15.166	1.0066,52	8
AT04	4562	043	041	X	70	16.273	24.172	43.919	1.0086,26	8
AT04	4563	043	041	X	71	56.655	45.988	44.3	1.0076,53	8
AT04	4564	043	041	X	71	44.653	15.572	21.500	1.0081,92	8
AT04	4565	043	041	X	71	13.915	34.012	32.537	1.0076,95	8
AT04	4566	043	041	X	71	18.894	23.324	28.549	1.0069,91	8
AT04	4567	043	041	X	72	25.942	27.526	52.380	1.0080,30	8
AT04	4568	043	041	X	72	50.444	15.097	54.32	1.0070,66	8
AT04	4569	043	041	X	72	67.258	38.530	40.380	1.0067,91	8
AT04	4570	043	041	X	72	13.119	23.916	-2.569	1.0057,58	8
AT04	4571	043	041	X	73	27.753	4.319	2.523	1.0068,14	8
AT04	4572	043	041	X	73	15.049	27.612	28.046	1.0071,85	8
AT04	4573	043	041	X	73	40.356	31.175	58.800	1.0077,21	8
AT04	4574	043	041	X	73	44.716	9.064	34.267	1.0056,22	8
AT04	4575	043	041	X	74	16.995	33.147	12.393	1.0074,77	8
AT04	4576	043	041	X	74	21.394	18.527	43.796	1.0077,10	8
AT04	4577	043	041	X	74	-0.275	3.264	2.271	1.0089,93	8
AT04	4578	043	041	X	74	22.139	35.199	17.275	1.0071,33	8
AT04	4579	043	041	X	74	23.877	44.987	16.233	1.0091,10	8
AT04	4580	043	041	X	74	41.289	9.005	3.932	1.0071,97	8
AT04	4581	043	041	X	75	38.329	57.673	44.241	1.0064,90	8
AT04	4582	043	041	X	75	18.910	30.958	52.593	1.0093,30	8
AT04	4583	043	041	X	75	68.020	36.610	50.288	1.0086,49	8
AT04	4584	043	041	X	75	22.139	35.199	17.275	1.0071,33	8
AT04	4585	043	041	X	76	61.482	44.510	42.192	1.0077,48	8
AT04	4586	043	041	X	76	22.107	41.072	47.776	1.0060,73	8
AT04	4587	043	041	X	76	2.634	-11.318	3.949	1.0069,96	8
AT04	4588	043	041	X	77	32.187	5.643	25.223	1.0076,13	8
AT04	4589	043	041	X	77	67.602	33.066	31.363	1.0072,25	8
AT04	4590	043	041	X	77	10.204	44.589	25.866	1.0064,86	8
AT04	4591	043	041	X	77	22.754	10.234	24.760	1.0066,60	8
AT04	4592	043	041	X	77	65.372	35.387	54.026	1.0068,26	8
AT04	4593	043	041	X	78	61.952	23.010	40.260	1.0064,44	8
AT04	4594	043	041	X	78	5.161	-0.757	6.920	1.0082,43	8
AT04	4595	043	041	X	78	57.524	45.787	43.333	1.0068,47	8
AT04	4596	043	041	X	79	27.601	31.115	24.743	1.00100,00	8
AT04	4597	043	041	X	79	13.772	31.115	20.243	1.0057,33	8
AT04	4598	043	041	X	79	58.663	23.880	36.310	1.0071,62	8
AT04	4599	043	041	X	79	22.310	10.775	17.577	1.0064,41	8
AT04	4600	043	041	X	80	64.430	36.300	57.179	1.0081,60	8
AT04	4601	043	041	X	80	51.348	32.222	6.950	1.0086,83	8
AT04	4602	043	041	X	80	28.165	8.846	53.068	1.0071,08	8
AT04	4603	043	041	X	80	65.757	27.493	38.760	1.0048,10	8
AT04	4604	043	041	X	81	45.269	12.874	37.874	1.0050,66	8
AT04	4605	043	041	X	81					
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AT04	4609	043	041	X	81					
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AT04	4611	043	041	X	81					
AT04	4612	043	041	X	81					
AT04	4613	043	041	X	81					
AT04	4614	043	041	X	81					
AT04	4615	043	041	X	81					
AT04	4616	043	041	X	81					
AT04	4617	043	041	X	81					
AT04	4618	043	041	X	81					
AT04	4619	043	041	X	81					
AT04	4620	043	041	X	81					
AT04	4621	043	041	X	81					
AT04	4622	043	041	X	81					
AT04	4623	043	041	X	81					
AT04	4624	043	041	X	81					
AT04	4625	043	041	X	81					
AT04	4626	043	041	X	81					
AT04	4627	043	041	X	81					
AT04	4628	043	041	X	81					
AT04	4629	043	041	X	81					
AT04	4630	043	041	X	81					
AT04	4631	043	041	X	81					
AT04	4632	043	041	X	81					
AT04	4633	043	041	X	81					
AT04	4634	043	041	X	81					
AT04	4635	043	041	X	81					
AT04	4636	043	041	X	81					
AT04	4637	043	041	X	81					
AT04	4638	043	041	X	81					
AT04	4639	043	041	X	81					
AT04	4640	043	041	X	81					
AT04	4641	043	041	X	81					
AT04	4642	043	041	X	81					
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AT04	4644	043	041	X	81					
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AT04	4648	043	041	X	81					
AT04	4649	043	041	X	81					
AT04	4650	043	041	X	81					
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AT04	4660	043	041	X	81					
AT04	4661	043	041	X	81					
AT04	4662	043	041	X	81					
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AT04	4664	043	041	X	81					
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AT04	4667	043	041	X	81					
AT04	4668	043	041	X	81					
AT04	4669	043	041	X	81					
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AT04	4684	043	041	X	81					
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AT04	4697	043	041	X	81					
AT04	4698	043	041	X	81					
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AT04	4704	043	041	X	81					
AT04	4705	043	041	X	81					
AT04	4706	043	041	X	81					
AT04	4707	043	041	X	81					
AT04	4708	043	041	X	81					
AT04	4709	043	041	X	81					
AT04	4710	043	041	X	81					
AT04	4711	043	041	X	81					
AT04										

AlOH	6665	043	WAT	X	90	39,112	6,740	5,054	1,00	66,72	8
AlOH	6666	044	WAT	X	90	43,364	57,890	49,964	1,00	71,30	8
AlOH	6667	046	WAT	X	90	16,187	17,842	27,844	1,00	71,63	8
AlOH	6668	047	WAT	X	90	22,913	3,223	6,101	1,00	63,34	8
AlOH	6669	049	WAT	X	91	0	23,117	18,644	1,00	68,95	8
AlOH	6670	041	WAT	X	91	0	14,144	12,297	1,00	68,45	8
AlOH	6671	042	WAT	X	91	46,758	22,374	17,228	1,00	68,45	8
AlOH	6672	043	WAT	X	91	50,310	39,246	9,155	1,00	68,48	8
AlOH	6673	045	WAT	X	91	14,832	31,811	-1,674	1,00	65,32	8
AlOH	6674	046	WAT	X	91	39,568	22,971	59,682	1,00	94,75	8
AlOH	6675	048	WAT	X	92	28,305	37,474	53,688	1,00	64,82	8
AlOH	6676	041	WAT	X	92	16,802	3,151	15,577	1,00	68,70	8
AlOH	6677	044	WAT	X	92	39,706	2,064	9,900	1,00	62,54	8
AlOH	6678	044	WAT	X	92	37,932	10,010	23,873	1,00	62,54	8
AlOH	6679	045	WAT	X	92	37,872	59,284	31,560	1,00	64,40	8
AlOH	6680	048	WAT	X	92	16,587	37,900	45,458	1,00	57,48	8
AlOH	6681	049	WAT	X	92	15,454	6,971	31,450	1,00	62,04	8
AlOH	6682	045	WAT	X	93	15,322	4,192	42,861	1,00	68,46	8
AlOH	6683	045	WAT	X	93	18,754	23,198	42,861	1,00	68,46	8
AlOH	6684	046	WAT	X	93	20,937	46,805	43,439	1,00	65,25	8
AlOH	6685	048	WAT	X	93	28,767	42,761	53,085	1,00	51,35	8
AlOH	6686	040	WAT	X	94	32,517	16,473	33,381	1,00	60,16	8
AlOH	6687	040	WAT	X	94	26,652	4,800	29,351	1,00	63,33	8
AlOH	6688	045	WAT	X	94	26,652	4,800	29,351	1,00	63,33	8
AlOH	6689	045	WAT	X	94	25,662	19,485	5,299	1,00	59,23	8
AlOH	6690	045	WAT	X	94	43,661	12,692	20,184	1,00	65,23	8
AlOH	6691	046	WAT	X	94	17,439	46,586	41,518	1,00	64,21	8
AlOH	6692	047	WAT	X	94	35,133	15,487	30,639	1,00	49,75	8
AlOH	6693	048	WAT	X	94	36,346	8,698	18,844	1,00	48,58	8
AlOH	6694	048	WAT	X	95	40,818	8,165	40,656	1,00	56,86	8
AlOH	6695	041	WAT	X	95	40,818	21,166	25,435	1,00	53,69	8
AlOH	6696	042	WAT	X	95	18,439	14,065	35,435	1,00	51,44	8
AlOH	6697	043	WAT	X	95	51,587	38,457	41,331	1,00	54,04	8
AlOH	6698	044	WAT	X	95	50,107	29,401	17,255	1,00	54,00	8
AlOH	6699	045	WAT	X	95	8,218	14,744	20,596	1,00	54,95	8
AlOH	6700	046	WAT	X	95	40,674	47,760	57,927	1,00	54,91	8

## CLAIMS

1. A method of constructing a variant of a parent Termamyl-like  $\alpha$ -amylase, which variant has  $\alpha$ -amylase activity and at least one altered property as compared to said parent  $\alpha$ -amylase, which method comprises

i) analysing the structure of the parent Termamyl-like  $\alpha$ -amylase to identify at least one amino acid residue or at least one structural part of the Termamyl-like  $\alpha$ -amylase structure, which amino acid residue or structural part is believed to be of relevance for altering said property of the parent Termamyl-like  $\alpha$ -amylase (as evaluated on the basis of structural or functional considerations),

15

ii) constructing a Termamyl-like  $\alpha$ -amylase variant, which as compared to the parent Termamyl-like  $\alpha$ -amylase, has been modified in the amino acid residue or structural part identified in i) so as to alter said property, and

20

iii) testing the resulting Termamyl-like  $\alpha$ -amylase variant for said property.

2. The method according to claim 1, wherein the property to be altered is selected from the group consisting of substrate specificity, substrate binding, substrate cleavage pattern, temperature stability, pH dependent activity, pH dependent stability (especially increased stability at low (e.g. pH<6) or high (e.g. pH>9) pH values), stability towards oxidation,  $\text{Ca}^{2+}$ -dependency and specific activity.

3. The method according to claim 1 or 2, wherein the property to be altered is the calcium ion dependency and the structural part to be modified is selected from the group consisting of the C domain, the interface between the A and B domain, the interface between the A and C domain, or the interaction to a calcium binding site of the Termamyl-like  $\alpha$ -amylase.

4. The method according to claim 1 or 2, wherein the property to be altered is the substrate cleavage pattern and the structural part to be modified is located within 10Å from an amino acid residue of the substrate binding site.

5

5. A method of constructing a variant of a parent Termamyl-like  $\alpha$ -amylase, which variant has  $\alpha$ -amylase activity and one or more altered properties as compared to said parent  $\alpha$ -amylase, which method comprises

- 10 i) comparing the three-dimensional structure of the Termamyl-like  $\alpha$ -amylase with the structure of a non-Termamyl-like  $\alpha$ -amylase,
- ii) identifying a part of the Termamyl-like  $\alpha$ -amylase structure which is different from the non-Termamyl-like  $\alpha$ -amylase
- 15 structure and which from structural or functional considerations is contemplated to be responsible for differences in one or more properties of the Termamyl-like and non-Termamyl-like  $\alpha$ -amylase, and
- iii) modifying the part of the Termamyl-like  $\alpha$ -amylase
- 20 identified in ii) whereby a Termamyl-like  $\alpha$ -amylase variant is obtained, one or more properties of which differ from the parent Termamyl-like  $\alpha$ -amylase.

6. The method according to claim 6, wherein, in step iii), the

25 part of the Termamyl-like  $\alpha$ -amylase is modified so as to resemble the corresponding part of the non-Termamyl-like  $\alpha$ -amylase.

7. The method according to claim 5 or 6, wherein, in step iii),

30 the modification is accomplished by deleting one or more amino acid residues of the part of the Termamyl-like  $\alpha$ -amylase to be modified; by replacing one or more amino acid residues of the part of the Termamyl-like  $\alpha$ -amylase to be modified with the amino acid residues occupying corresponding positions in the

35 non-Termamyl-like  $\alpha$ -amylase; or by insertion of one or more amino acid residues present in the non-Termamyl-like  $\alpha$ -amylase into a corresponding position in the Termamyl-like  $\alpha$ -amylase.

8. The method according to any of claims 5-7, wherein the non-Termamyl-like  $\alpha$ -amylase structure is the structure of a fungal  $\alpha$ -amylase or a mammalian  $\alpha$ -amylase.
- 5 9. The method according to claim 8, wherein the non-Termamyl-like  $\alpha$ -amylase is the *Aspergillus oryzae* TAKA  $\alpha$ -amylase, the *A. niger* acid  $\alpha$ -amylase, the *Bacillus subtilis*  $\alpha$ -amylase or the pig pancreatic  $\alpha$ -amylase.
- 10 10. The method according to any of claims 1-9, wherein the parent Termamyl-like  $\alpha$ -amylase is derived from a strain of *Bacillus*.
11. The method according to claim 10, wherein the parent  $\alpha$ -  
15 amylase is derived from a strain of a *B. licheniformis*, *B. amyloliquefaciens*, *B. stearothermophilus* or a strain from an alkalophilic *Bacillus* sp. such as NCIB 12289, NCIB 12512 or NCIB 12513.
- 20 12. The method according to any of claims 1-11, wherein the parent  $\alpha$ -amylase is a hybrid  $\alpha$ -amylase comprising a combination of partial amino acid sequences derived from at least two  $\alpha$ -amylases, of which one is a Termamyl-like  $\alpha$ -amylase and the other(s) are, e.g., from a microbial and/or a mammalian  $\alpha$ -  
25 amylase.
13. The method according to any of claims 5-12, wherein the part of the parent Termamyl-like  $\alpha$ -amylase to be modified and identified in step ii) is loop 1, loop 2, loop 3 and/or loop 8  
30 of the parent  $\alpha$ -amylase.
13. A method of constructing a variant of a parent Termamyl-like  $\alpha$ -amylase, which has a decreased calcium ion dependency as compared to said parent, which method comprises:
- 35 i) identifying an amino acid residue within 10Å from a  $\text{Ca}^{2+}$  binding site of a Termamyl-like  $\alpha$ -amylase in a model of the three-dimensional structure of said  $\alpha$ -amylase, which from

- structural or functional considerations is believed to be responsible for a non-optimal calcium ion interaction,
- ii) constructing a variant in which said amino acid residue is replaced with another amino acid residue which from structural or functional considerations is believed to be important for establishing a higher  $\text{Ca}^{2+}$  binding affinity, and
- iii) testing the  $\text{Ca}^{2+}$  dependency of the resulting Termamyl-like  $\alpha$ -amylase variant.
- 10 14. A method of constructing a variant of a parent Termamyl-like  $\alpha$ -amylase which variant has  $\alpha$ -amylase activity and an altered pH dependent activity, which method comprises
- i) in a three-dimensional structure of the Termamyl-like  $\alpha$ -amylase in question, identifying an amino acid residue within 15 15Å from an active site residue, in particular 10Å from an active site residue, which amino acid residue is contemplated to be involved in electrostatic or hydrophobic interactions with an active site residue,
- 20 ii) replacing, in the structure, said amino acid residue with an amino acid residue which changes the electrostatic and/or hydrophobic surroundings of an active site residue and evaluating the accomodation of the amino acid residue in the
- 25 structure,
- iii) optionally repeating step i) and/or ii) until an amino acid replacement has been identified which is accomodated into the structure,
- 30 iv) constructing a Termamyl-like  $\alpha$ -amylase variant resulting from steps i), ii) and optionally iii) and testing the pH dependent activity of said variant.
- 35 15. A method of increasing the thermostability and/or altering the temperature optimum of a parent Termamyl-like  $\alpha$ -amylase, which method comprises

- i) identifying an internal hole or a crevice of the parent Termamyl-like  $\alpha$ -amylase in the three-dimensional structure of said  $\alpha$ -amylase,
- ii) replacing, in the structure, one or more amino acid residues in the neighbourhood of the hole or crevice identified in i) with another amino acid residue which from structural or functional considerations is believed to increase the hydrophobic interaction and to fill out or reduce the size of the hole or crevice,
- 10 iii) constructing a Termamyl-like  $\alpha$ -amylase variant resulting from step ii) and testing the thermostability and/or temperature optimum of the variant.

16. A method of constructing a variant of a Termamyl-like  $\alpha$ -amylase which has a reduced ability to cleave a substrate close to the branching point, which method comprises

- i) identifying the substrate binding area of the parent Termamyl-like  $\alpha$ -amylase in a model of the three-dimensional structure of said  $\alpha$ -amylase,

- ii) replacing, in the model, one or more amino acid residues of the substrate binding area of the cleft identified in i), which is/are believed to be responsible for the cleavage pattern of the parent  $\alpha$ -amylase, with another amino acid residue which from structural considerations is believed to result in an altered substrate cleavage pattern, or deleting one or more amino acid residues of the substrate binding area contemplated to introduce favourable interactions to the substrate or adding

- iii) constructing a Termamyl-like  $\alpha$ -amylase variant resulting from step ii) and testing the substrate cleavage pattern of the variant.

17. The method according to any of the preceeding claims, in which the  $\alpha$ -amylase variant is obtained by cultivating a

microorganism comprising a DNA sequence encoding the variant under conditions which are conducive for producing the variant, and optionally subsequently recovering the variant from the resulting culture broth.

5

18. A variant of a parent Termamyl-like  $\alpha$ -amylase, in which variant at least one amino acid residue of the parent  $\alpha$ -amylase, which is/are present in a fragment corresponding to the amino acid fragment 44-57 of the amino acid sequence of SEQ ID No. 4, has been deleted or replaced with one or more amino acid residues which is/are present in a fragment corresponding to the amino acid fragment 66-84 of the amino acid sequence shown in SEQ ID No. 10, or in which one or more additional amino acid residues has been added using the relevant part of SEQ ID No. 10 or a corresponding part of another Fungamyl-like  $\alpha$ -amylase as a template.

19. A variant of a parent Termamyl-like  $\alpha$ -amylase, which variant has a region which, when the amino acid sequence of variant is aligned most closely with the amino acid sequence of the said parent  $\alpha$ -amylase, occupies the same position as the portion from residue X to residue Y of SEQ ID No 4, the said region having at least 80% sequence homology with the part of SEQ ID No 10 extending from residue Z to residue V of SEQ ID No 10, wherein

- X is the amino acid residue occupying position 44, 45, 46, 47 or 48 of SEQ ID No. 4,  
Y is the amino acid residue occupying position 51, 52, 53, 54, 55, 56 or 57 of SEQ ID No. 4,  
Z is the amino acid residue occupying position 66, 67, 68, 69 or 70 of SEQ ID No. 10, and  
V is the amino acid residue occupying position 78, 79, 80, 81, 82, 83 or 84 of SEQ ID No. 10.

20. The variant according to claim 18 or 19, wherein X is the amino acid residue occupying position 48 and Y the amino acid residue occupying position 51 of SEQ ID NO 4 and Z is the amino

acid residue occupying position 70 and V the amino acid residue occupying position 78 in SEQ ID No 10.

21. A variant of a parent Termamyl-like  $\alpha$ -amylase, in which  
5 variant at least one of the amino acid residues of the parent  
 $\alpha$ -amylase, which is/are present in an amino acid fragment  
corresponding to the amino acid fragment 195-202 of the amino  
acid sequence of SEQ ID No. 4, has been deleted or replaced  
with one or more of the amino acid residues which is/are  
10 present in an amino acid fragment corresponding to the amino  
acid fragment 165-177 of the amino acid sequence shown in SEQ  
ID No. 10, or in which one or more additional amino acid  
residues has been added using the relevant part of SEQ ID No.  
10 or a corresponding part of another Fungamyl-like  $\alpha$ -amylase  
15 as a template.

22. A variant of a parent Termamyl-like  $\alpha$ -amylase, which  
variant has a region which, when the amino acid sequence of  
variant is aligned most closely with the amino acid sequence of  
20 the said parent  $\alpha$ -amylase, occupies the same position as the  
portion from residue X to residue Y of SEQ ID No 4, the said  
region having at least 80%, such as 90% sequence homology with  
the part of SEQ ID No 10 extending from residue Z to residue V  
of SEQ ID No 10, wherein  
25 X is the amino acid occupying position 195 or 196 of SEQ ID No.  
4,

Y is the amino acid residue occupying position 198, 199, 200,  
201, or 202 of SEQ ID No. 4,

30

Z is the amino acid residue occupying position 165 or 166 of  
SEQ ID No. 10, and

V is the amino acid residue occupying position 173, 174, 175,  
35 176 or 177 of SEQ ID No. 10.

23. The variant according to claim 21 or 22, in which the amino  
acid fragment of the parent  $\alpha$ -amylase, which corresponds to

amino acid residues 196-198 of SEQ ID No. 4, has been replaced with the amino acid fragment corresponding to amino acid residues 166-173 of the amino acid sequence shown in SEQ ID No. 10.

5

24. A variant of a parent Termamyl-like  $\alpha$ -amylase, in which variant at least one of the amino acid residues of the parent  $\alpha$ -amylase, which is/are present in a fragment corresponding to the amino acid fragment 117-185 of the amino acid sequence of  
10 SEQ ID No. 4, has/have been deleted or replaced with one or more of the amino acid residues, which is/are present in an amino acid fragment corresponding to the amino acid fragment 98-210 of the amino acid sequence shown in SEQ ID No. 10, or in which one or more additional amino acid residues has been added  
15 using the relevant part of SEQ ID No. 10 or a corresponding part of another Fungamyl-like  $\alpha$ -amylase as a template.

25. A variant of a parent Termamyl-like  $\alpha$ -amylase, which variant has a region which, when the amino acid sequence of  
20 variant is aligned most closely with the amino acid sequence of the said parent  $\alpha$ -amylase, occupies the same position as the portion from residue X to residue Y of SEQ ID No 4, the said region having at least 80%, such as at least 90% sequence homology with the part of SEQ ID No 10 extending from residue  
25 Z to residue V of SEQ ID No 10, wherein

X is the amino acid occupying position 117, 118, 119, 120 or 121 of SEQ ID No. 4,

30 Y is the amino acid occupying position 181, 182, 183, 184 or 185 of SEQ ID No. 4,

Z is the amino acid occupying position 98, 99, 100, 101, 102 of SEQ ID No. 10, and

35

V is the amino acid occupying position 206, 207, 208, 209 or 210 of SEQ ID No. 10.

26. The variant according to claim 24 or 25, in which an amino acid fragment of the parent  $\alpha$ -amylase, which corresponds to amino acid residues 121-181 of SEQ ID No. 4, has been replaced with the amino acid fragment corresponding to amino acid residues 102-206 of the amino acid sequence shown in SEQ ID No. 10.

27. A variant of a parent Termamyl-like  $\alpha$ -amylase, in which variant at least one of the amino acid residues of the parent  $\alpha$ -amylase, which is/are present in a fragment corresponding to the amino acid fragment 117-181 of the amino acid sequence of SEQ ID No. 4, has/have been deleted or replaced with one or more of the amino acid residues, which is/are present in an amino acid fragment corresponding to the amino acid fragment to 98-206 of the amino acid sequence shown in SEQ ID No. 10, or in which one or more additional amino acid residues has been added using the relevant part of SEQ ID No. 10 or a corresponding part of another Fungamyl-like  $\alpha$ -amylase as a template.

28. A variant of a parent Termamyl-like  $\alpha$ -amylase, which variant has a region which, when the amino acid sequence of variant is aligned most closely with the amino acid sequence of the said parent  $\alpha$ -amylase, occupies the same position as the portion from residue X to residue Y of SEQ ID No 4, the said region having at least 80%, such as at least 90% sequence homology with the part of SEQ ID No 10 extending from residue Z to residue V of SEQ ID No 10, wherein X is the amino acid occupying position 117, 118, 119, 120 or 121 of SEQ ID No. 4,

Y is the amino acid occupying position 174, 175, 176 or 177 of SEQ ID No. 4,

Z is the amino acid occupying position 98, 99, 100, 101, 102 of SEQ ID No. 10, and

V is the amino acid occupying position 199, 200, 201 or 202 of SEQ ID No. 10.

29. The variant according to claim 27 or 28, in which the amino acid fragment of the parent  $\alpha$ -amylase, which corresponds to amino acid residues 121-174 of SEQ ID No. 4, has been replaced with the amino acid fragment corresponding to amino acid residues 102-199 of the amino acid sequence shown in SEQ ID No. 10.

10

30. A variant of a parent Termamyl-like  $\alpha$ -amylase, in which variant at least one of the amino acid residues of the parent  $\alpha$ -amylase, which is/are present in an amino acid fragment corresponding to the amino acid fragment 12-19 of the amino acid sequence of SEQ ID No. 4, has/have been deleted or replaced with one or more of the amino acid residues, which is/are present in an amino acid fragment which corresponds to the amino acid fragment 28-42 of SEQ ID No. 10, or in which one or more additional amino acid residues has/have been inserted using the relevant part of SEQ ID No. 10 or a corresponding part of another Fungamyl-like  $\alpha$ -amylase as a template.

31. A variant of a parent Termamyl-like  $\alpha$ -amylase, which variant has a region which, when the amino acid sequence of variant is aligned most closely with the amino acid sequence of the said parent  $\alpha$ -amylase, occupies the same position as the portion from residue X to residue Y of SEQ ID No 4, the said region having at least 80%, such as at least 90% sequence homology with the part of SEQ ID No 10 extending from residue Z to residue V of SEQ ID No 10, wherein

X is the amino acid occupying position 12, 13 or 14 of SEQ ID No. 4,

Y is the amino acid occupying position 15, 16, 17, 18 or 19 of SEQ ID No. 4,

32 Z is the amino acid occupying position 28, 29, 30, 31 or 32 of SEQ ID No. 10, and

V is an amino acid residue corresponding to the amino acid occupying position 38, 39, 40, 41 or 42 of SEQ ID No. 10.

32. The variant according to claim 30 or 31, in which the amino acid fragment of the parent  $\alpha$ -amylase, which corresponds to amino acid residues 14-15 of SEQ ID No. 4, has been replaced with the amino acid fragment corresponding to amino acid residues 32-38 of the amino acid sequence shown in SEQ ID No. 10.

33. A variant of a parent Termamyl-like  $\alpha$ -amylase, in which variant at least one of the amino acid residues of the parent  $\alpha$ -amylase, which is present in a fragment corresponding to amino acid residues 7-23 of the amino acid sequence of SEQ ID No. 4, has/have been deleted or replaced with one or more amino acid residues, which is/are present in an amino acid fragment corresponding to amino acid residues 13-45 of the amino acid sequence shown in SEQ ID No. 10, or or in which one or more additional amino acid residues has/have been inserted using the relevant part of SEQ ID No. 10 or a corresponding part of another Fungamyl-like  $\alpha$ -amylase as a template.

34. A variant of a parent Termamyl-like  $\alpha$ -amylase, which variant has a region which, when the amino acid sequence of variant is aligned most closely with the amino acid sequence of the said parent  $\alpha$ -amylase, occupies the same position as the portion from residue X to residue Y of SEQ ID No 4, the said region having at least 80%, such as at least 90% sequence homology with the part of SEQ ID No 10 extending from residue Z to residue V of SEQ ID No 10, wherein X is the amino acid occupying position 7 or 8 of SEQ ID No. 4,

Y is the amino acid occupying position 18, 19, 20, 21, 22 or 23 of SEQ ID No. 4,

Z is the amino acid occupying position 13 or 14 of SEQ ID No. 10, and

V is the amino acid occupying position 40, 41, 42, 43, 44 or 45 of SEQ ID No. 10.

35. The variant according to claim 33 or 34, in which the amino acid fragment of the parent  $\alpha$ -amylase, which corresponds to amino acid residues 8-18 of SEQ ID No. 4, has been replaced with the amino acid fragment corresponding to amino acid residues 14-40 of the amino acid sequence shown in SEQ ID No. 10.

36. A variant of a parent Termamyl-like  $\alpha$ -amylase, in which variant at least one of the amino acid residues of the parent  $\alpha$ -amylase, which is present in a fragment corresponding to amino acid residues 322-346 of the amino acid sequence of SEQ ID No. 2, has/have been deleted or replaced with one or more amino acid residues, which is/are present in an amino acid fragment corresponding to amino acid residues 291-313 of the amino acid sequence shown in SEQ ID No. 10, or or in which one or more additional amino acid residues has/have been inserted using the relevant part of SEQ ID No. 10 or a corresponding part of another Fungamyl-like  $\alpha$ -amylase as a template.

37. A variant of a parent Termamyl-like  $\alpha$ -amylase, which variant has a region which, when the amino acid sequence of variant is aligned most closely with the amino acid sequence of the said parent  $\alpha$ -amylase, occupies the same position as the portion from residue X to residue Y of SEQ ID No 2, the said region having at least 80% sequence homology with the part of SEQ ID No 10 extending from residue Z to residue V of SEQ ID No 10, wherein

X is the amino acid occupying position 322, 323, 324 or 325 of SEQ ID No. 2,

Y is the amino acid occupying position 343, 344, 345 or 346 of SEQ ID No. 2,

Z is the amino acid occupying position 291, 292, 293 or 294 of SEQ ID No. 10, and

V is the amino acid occupying position 310, 311, 312 or 313 of SEQ ID No. 10.

38. The variant according to claim 36 or 37, in which the amino acid fragment of the parent  $\alpha$ -amylase, which corresponds to amino acid residues 325-345 of SEQ D No. 2, has been replaced with the amino acid fragment corresponding to amino acid residues 294-313 of the amino acid sequence shown in SEQ ID No. 10.

39. A variant of a parent Fungamyl-like  $\alpha$ -amylase, in which variant at least one of the amino acid residues of the parent  $\alpha$ -amylase, which is/are present in an amino acid fragment corresponding to amino acid residues 291-313 of the amino acid sequence of SEQ ID No. 10, has/have been deleted or replaced with one or more of the amino acid residues, which is/are present in an amino acid fragment corresponding to amino acid residues 98-210 of the amino acid sequence shown in SEQ ID No. 4, or in which one or more additional amino acid residues has/have been inserted using the relevant part of SEQ ID No. 4 or a corresponding part of another Termamyl-like  $\alpha$ -amylase as a template.

20

40. A variant of a parent Fungamyl-like  $\alpha$ -amylase, which variant has a region which, when the amino acid sequence of variant is aligned most closely with the amino acid sequence of the said parent  $\alpha$ -amylase, occupies the same position as the portion from residue X to residue Y of SEQ ID No 10, the said region having at least 80%, such as at least 90% sequence homology with the part of SEQ ID No 10 extending from residue Z to residue V of SEQ ID No 4, wherein X is the amino acid occupying position 117, 118, 119, 120 or 121 of SEQ ID No. 10,

Y is the amino acid occupying position 181, 182, 183, 184 or 185 of SEQ ID No. 10,

35 Z is the amino acid occupying position 98, 99, 100, 101 or 102 of SEQ ID No. 4, and

V is the amino acid occupying position 206, 207, 208, 209 or 210 of SEQ ID No. 4.

41. The variant according to claim 39 or 40, in which the amino acid fragment of the parent  $\alpha$ -amylase, which corresponds to amino acid residues 121-181 of SEQ ID No. 10, has been replaced with the amino acid fragment corresponding to amino acid residues 102-206 of the amino acid sequence shown in SEQ ID No. 4.

10

42. A variant according to any of claims 39-41, in which the amino acid fragment of the parent  $\alpha$ -amylase, which corresponds to amino acid residues 121-174 of SEQ ID No. 10, has been replaced with the amino acid fragment corresponding to amino acid residues 102-199 of the amino acid sequence shown in SEQ ID No. 4.

43. A variant of a parent Fungamyl-like  $\alpha$ -amylase, in which an amino acid fragment corresponding to amino acid residues 181-184 of the amino acid sequence shown in SEQ ID No. 10 has been deleted.

45. A variant of a parent Termamyl-like  $\alpha$ -amylase, which exhibits  $\alpha$ -amylase activity and which has a decreased  $\text{Ca}^{2+}$  dependency as compared to the parent  $\alpha$ -amylase.

46. A variant according to claim 45, which comprises a mutation in a position corresponding to at least one of the following positions in SEQ ID NO 2:

30 N104, A349, I479, L346, I430, N457, K385, F350, I411, H408 or G303, in particular a mutation corresponding to

N104D;

A349C+I479C;

L346C+I430C;

35 N457D,E;

N457D,E+K385R;

F350D,E+I430R,K;

F350D,E+I411R,K;

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H408Q,E,N,D; and/or  
G303N,D,Q,E.

47. A variant of a parent Termamyl-like  $\alpha$ -amylase which  
5 exhibits a higher activity below the pH optimum than the parent  
 $\alpha$ -amylase, which variant comprises a mutation of an amino acid  
residue corresponding to at least one of the following  
positions of the *B. licheniformis*  $\alpha$ -amylase (SEQ ID NO 2):  
E336, Q333, P331, I236, V102, A232, I103, L196, in particular  
10 at least one of the following mutations:

E336R,K;  
Q333R,K; P331R,K;  
V102R,K,A,T,S,G;  
I236K,R,N;  
15 I103K,R;  
L196K,R; and/or  
A232T,S,G.

48. A variant of a parent Termamyl-like  $\alpha$ -amylase which  
20 exhibits a higher activity above the pH optimum than the parent  
 $\alpha$ -amylase, which variant comprises a mutation of an amino acid  
residue corresponding to at least one of the following  
positions of the *B. licheniformis*  $\alpha$ -amylase (SEQ ID NO 2):  
N236, H281 and/or Y273, in particular one of the following  
25 mutations:

N326I,Y,F,L,V;  
H281F,I,L; and/or  
Y273F,W.

30 49. A variant of a parent Termamyl-like  $\alpha$ -amylase which  
exhibits  $\alpha$ -amylase activity and which has an increased  
thermostability and/or altered temperature optimum as compared  
to the parent  $\alpha$ -amylase, which variant comprises a mutation of  
an amino acid residue corresponding to at least one of the  
35 following positions of the *B. licheniformis*  $\alpha$ -amylase (SEQ ID  
NO 2):

L61, Y62, F67, K106, G145, I212, S151, R214, Y150, F143, R146, L241, I236, L7, V259, F284, F350, F343, L427 and/or V481, in particular at least one of the following mutations:

L61W,V,F;

5 Y62W;

F67W;

K106R,F,W;

G145F,W

I212F,L,W,Y,R,K;

10 S151 replaced with any other amino acid residue and in particular with F,W,I or L;

R214W;

Y150R,K;

F143W;

15 R146W;

L241I,F,Y,W;

I236L,F,W,Y;

L7F,I,W;

V259F,I,L;

20 F284W;

F350W;

F343W;

L427F,L,W; and/or

V481,F,I,L,W.

25

50. A variant of a parent Termamyl-like  $\alpha$ -amylase, which exhibits  $\alpha$ -amylase activity and which has a reduced capability of cleaving an oligo-saccharide substrate close to the branching point as compared to the parent  $\alpha$ -amylase, which  
30 variant comprises a mutation of an amino acid residue corresponding to at least one of the following positions of the *B. licheniformis*  $\alpha$ -amylase (SEQ ID NO 2):

V54, D53, Y56, Q333 and/or G57, in particular at least one of  
35 the following mutations:

V54L,I,F,Y,W,R,K,H,E,Q;

D53L,I,F,Y,W;

Y,56W;

Q333W; and/or  
G57 to all possible amino acid residues.

51. The variant according to any of claims 17-50, wherein one  
5 or more proline residues present in the amino acid residues  
with which the parent  $\alpha$ -amylase is modified are replaced with  
a non-proline residue such as alanine.

52. The variant according to any of claims 17-51, wherein one  
10 or more cysteine residues present in the amino acid residues  
with which the parent  $\alpha$ -amylase is modified are replaced with  
a non-cysteine residue such as alanine.

53. A DNA construct comprising a DNA sequence encoding an  $\alpha$ -  
15 amylase variant according to any of claims 17-52.

54. A recombinant expression vector which carries a DNA con-  
struct according to Claim 53.

20 55. A cell which is transformed with a DNA construct according  
to Claim 53 or a vector according to Claim 54.

56. A cell according to Claim 55, which is a microorganism.

25 57. A cell according to Claim 56, which is a bacterium or a  
fungus.

58. The cell according to Claim 57, which is a grampositive  
bacterium such as *Bacillus subtilis*, *Bacillus licheniformis*,  
30 *Bacillus lentus*, *Bacillus brevis*, *Bacillus stearothermophilus*,  
*Bacillus alkalophilus*, *Bacillus amyloliquefaciens*, *Bacillus*  
*coagulans*, *Bacillus circulans*, *Bacillus lautus* or *Bacillus thu-*  
*ringiensis*.

35 59. Use of an  $\alpha$ -amylase variant according to any of claims 17-  
52 for washing and/or dishwashing.

60. Use of an  $\alpha$ -amylase variant according to any of claims 17-52 for desizing.

61. Use of an  $\alpha$ -amylase variant according to any of claims 17-52 for starch liquefaction.

62. A detergent additive comprising an  $\alpha$ -amylase variant according to any of claims 17-52, optionally in the form of a non-dusting granulate, stabilised liquid or protected enzyme.

10

63. A detergent additive according to Claim 62 which contains 0.02-200 mg of enzyme protein/g of the additive.

64. A detergent additive according to Claim 62 or 63, which additionally comprises another enzyme such as a protease, a lipase, a peroxidase, another amylolytic enzyme and/or a cellulase.

65. A detergent composition comprising an  $\alpha$ -amylase variant according to any of claims 17-52.

66. A detergent composition according to Claim 65 which additionally comprises another enzyme such as a protease, a lipase, a peroxidase, another amylolytic enzyme and/or a cellulase.

25

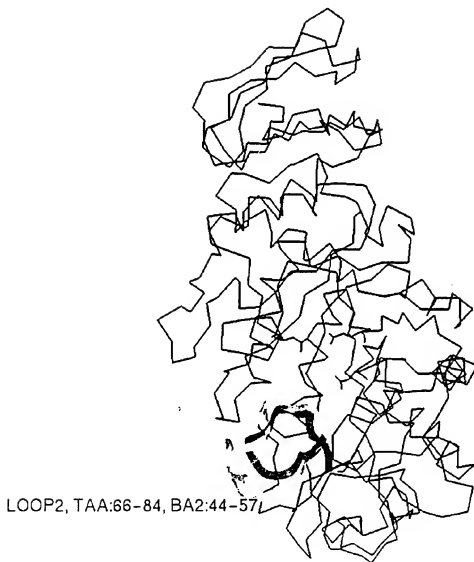
67. A manual or automatic dishwashing detergent composition comprising an  $\alpha$ -amylase variant according to any of claims 17-52.

68. A dishwashing detergent composition according to Claim 67 which additionally comprises another enzyme such as a protease, a lipase, a peroxidase, another amylolytic enzyme and/or a cellulase.

69. A manual or automatic laundry washing composition comprising an  $\alpha$ -amylase variant according to any of claims 17-52.

70. A laundry washing composition according to Claim 69, which additionally comprises another enzyme such as a protease, a lipase, a peroxidase, an amylolytic enzyme and/or a cellulase.

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**Fig. 1**

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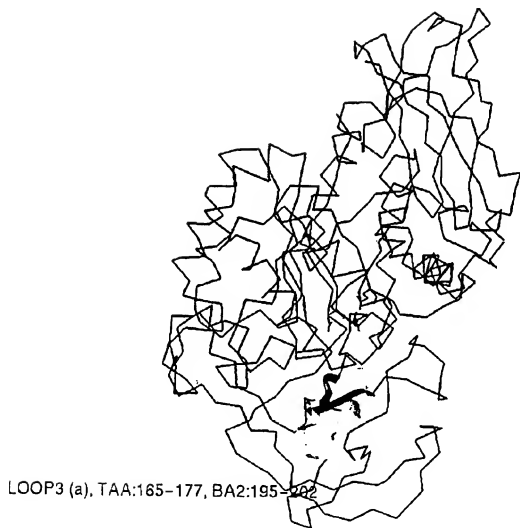
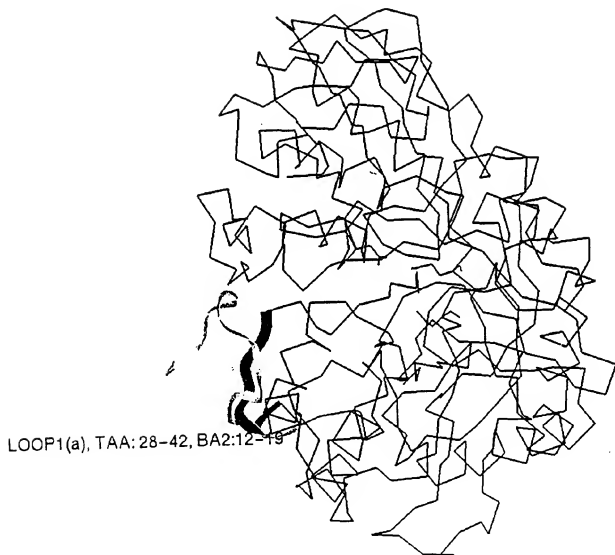


Fig. 2

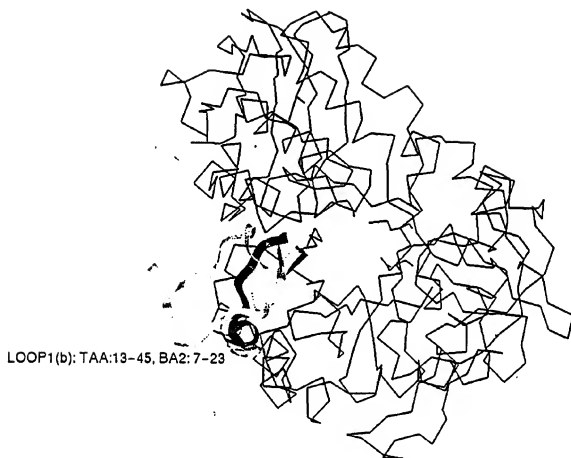
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**Fig. 3**

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**Fig. 4**

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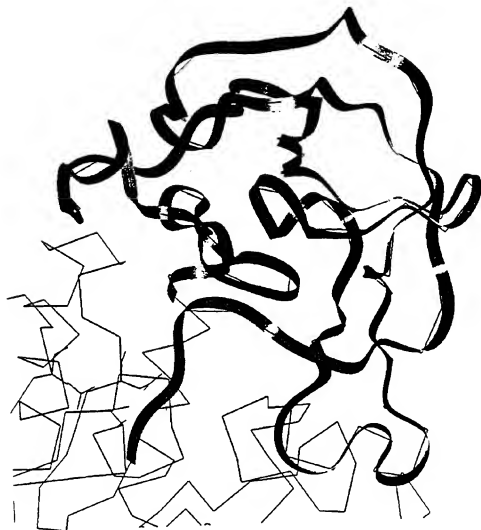
**Fig. 5****SUBSTITUTE SHEET (RULE 26)**

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LOOP8:TAA:291-313, BA2: 322-346

**Fig. 6**

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**Fig. 7**

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1  
CAT CAT AAT GGA ACA AAT GGT ACT ATG ATG CAA TAT TTC GAA TGG TAT TTG CCA AAT GAC  
H H N G T N G T M M Q Y F E W Y L P N D

21  
GGG AAT CAT TGG AAC AGG TTG AGG GAT GAC GCA GCT AAC TTA AAG AGT AAA GGG ATA ACA  
G N H W N R L R D D A A N L K S K G I T

41  
GCT GTA TGG ATC CCA CCT GCA TGG AAG GGG ACT TCC CAG AAT GAT GTA GGT TAT GGA GCC  
A V W I P P A W K G T S Q N D V G Y G A

61  
TAT GAT TTA TAT GAT CTT GGA GAG TTT AAC CAG AAG GGG ACG GTT CGT ACA AAA TAT GGA  
Y D L Y D L G E F N Q K G T V R T K Y G

81  
ACA CGC AAC CAG CTA CAG GCT CGC GTG ACC TCT TTA AAA AAT AAC GGC ATT CAG GTA TAT  
T R N Q L Q A A V T S L K N N G I Q V Y

101  
GGT GAT GTC GTC ATG AAT CAT AAA GGT GGA GCA GAT GGT ACG GAA ATT GTA AAT CGC GTA  
G D V V M N H K G G A D G T E I V N A V

121  
GAA GTG AAT CGG AGC AAC CGA AAC CAG GAA ACC TCA GGA GAG TAT GCA ATA GAA CGC TGG  
E V N R S N R N Q E T S G E Y A I E A W

141  
ACA AAG TTT GAT TTT CCT GGA AGA GGA AAT AAC CAT TCC AGC TTT AAG TGG CGC TGG TAT  
T K F D F P G R G N N H S S F K W R W Y

161  
CAT TTT GAT GGG ACA GAT TGG GAT CAG TCA CGC CAG CTT CAA AAC AAA ATA TAT AAA TTC  
H F D G T D W D Q S R Q L Q N K I Y K F

181  
AGG GGA ACA GGC AAG GCC TGG GAC TGG GAA GTC GAT ACA GAG AAT GGC AAC TAT GAC TAT  
R G T G K A W D W E V D T E N G N Y D Y

201  
CTT ATG TAT GCA GAC GTG GAT ATG GAT CAC CCA GAA GTA ATA CAT GAA CTT AGA AAC TGG  
L H Y A D V D H D H P E V I H E L R N W

221  
GGA GTG TGG TAT ACG AAT ACA CTG AAC CTT GAT GGA TTT AGA ATA GAT GCA GTG AAA CAT  
G V W Y T N T L N L D G F R I D A V X H

241  
ATA AAA TAT AGC TTT ACG AGA GAT TGG CTT ACA CAT GTG CGT AAC ACC ACA GGT AAA CCA  
I K Y S F T R D W L T H V R N T T G K P

261  
ATG TTT GCA GTG GCT GAG TTT TGG AAA AAT GAC CTT GGT GCA ATT GAA AAC TAT TTG AAT  
M F A V A E F W K N D L G A I E N Y L N

281  
AAA ACA AGT TGG AAT CAC TCG GTG TTT GAT GTT CCT CTC CAC TAT AAT TTG TAC AAT GCA  
K T S W N H S V F D V P L H Y N L Y N A

Fig. 8

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301  
TCT AAT AGC GGT GGT TAT TAT GAT ATG AGA AAT ATT TTA AAT GGT TCT GTG GTG CAA AAA  
S N S G G Y Y D M R N I L N G S V V Q K

321  
CAT CCA ACA CAT GCC GTT ACT TTT GTT GAT AAC CAT GAT TCT CAG CCC GGG GAA GCA TTG  
H P T H A V T F V D N H D S Q P G E A L

341  
GAA TCC TTT GTT CAA CAA TGG TTT AAA CCA CTT GCA TAT GCA TTG GTT CTG ACA AGG GAA  
E S F V Q Q W F K P L A Y A L V L T R E

361  
CAA GGT TAT CCT TCC GTA TTT TAT GGG GAT TAC TAC GGT ATC CCA ACC CAT GGT GTT CCG  
Q G Y P S V F Y G D Y Y G I P T H G V P

381  
GCT ATG AAA TCT AAA ATA GAC CCT CTT CTG CAG GCA CGT CAA ACT TTT GCC TAT GGT ACG  
A M K S K I D P L L Q A R Q T F A Y G T

401  
CAG CAT GAT TAC TTT GAT CAT CAT GAT ATT ATC GGT TGG ACA AGA GAG GGA AAT AGC TCC  
Q H D Y F D H H D I I G W T R E G N S S

421  
CAT CCA AAT TCA GGC CTT GCC ACC ATT ATG TCA GAT GGT CCA GGT GGT AAC AAA TGG ATG  
H P N S G L A T I M S D G P G G N X W M

441  
TAT GTG GGG AAA AAT AAA GCG GGA CAA GTT TGG AGA GAT ATT ACC GGA AAT AGG ACA GGC  
Y V G K N K A G Q V W R D I T G N R T G

261  
ACC GTC ACA ATT AAT GCA GAC GGA TGG GGT AAT TTC TCT GTT AAT GGA GGG TCC GTT TCG  
T V T I N A D G W G N F S V N G G S V S

481  
GTT TGG GTG AAG CAA TAA  
V W V K Q \*

Fig. 8 (cont.)

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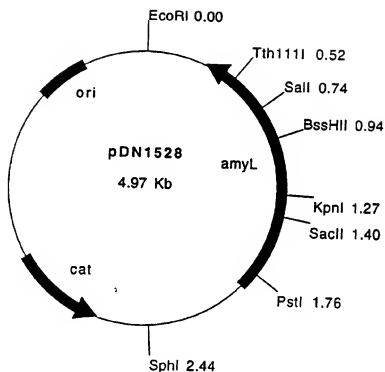


Fig. 9

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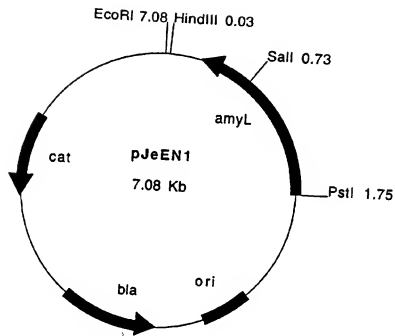


Fig. 10

1  
INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 96/00057

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C12N 9/28, C12N 15/56

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, CA, MEDLINE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	Dialog Information Services, File 5, BIOSIS PREVIEWS, Dialog accession no. 11619266, BIOSIS no. 98219266, Machius M et al: "Crystal structure of calcium-depleted Bacillus licheni- formis alpha-amylase at 2.2 Å resolution", & Journal of Molecular Biology 246 (4). 1995. 545-559  --	1-17
X	Dialog Information Services, file 155, MEDLINE, Dialog accession no. 08974640, MEDLINE accession no. 94289640, Svensson B: "Protein engineering in the alpha-amylase family: catalytic mechanism, substrate specificity, and stability", & Plant Mol Biol (NETHERLANDS) May 1994, 25 (2) p141-57  --	1-17

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

\* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" documents published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

5 July 1996

05 -07- 1996

Name and mailing address of the ISA

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The invention claimed relates to a method of constructing alpha-amylase variants with predetermined properties by comparing the three-dimensional structures of enzymes. The claims also include many alpha-amylase variants.

"A search for a special technical feature" as mentioned in PCT Rule 13.2 among the independent claims did not reveal a unifying, novel technical feature.

Accordingly, the following inventions were found:

- I Claims 1-17 focus on a method of constructing alpha-amylase variants by comparing the three-dimensional structure of a parent enzyme (Temamyl-like alpha-amylase) with another enzyme e.g. mammalian or fungal alpha-amylases. The differences in structure are compared with the differences in function, whereafter new variants with new predictable characteristics are produced.
- II Claims 45-46 directed to a alpha-amylase variant that has decreased  $\text{Ca}^{2+}$  dependency,
- III Claim 47 directed to a alpha-amylase variant that exhibits higher activity below the pH-optimum than the parent enzyme.
- IV Claim 48 directed to a alpha-amylase variant having an increased thermostability and/or altered temperature optimum.
- V Claim 50 directed to a variant having reduced capability of cleaving an oligo-saccharide substrate close to its branching point.

Due to the complex construction of the claims and the fact that the search so far has not covered all aspects of the invention, it may be that further non-unity remarks can appear. If further searches are done, references might appear which will give further a posteriori non-unity remarks.

Therefore, the search has been restricted to the first invention.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 96/00057

Claims 18-43 are directed to a number of different variants that are composed of several inventions. They are, however, so complex and broad that no meaningful search can be done, especially as no special characteristic is linked to the groups of variants. It is for example unlikely that claim 18 concerns one invention. It is not believable that a change in any amino acid in one fragment for one/or none of the amino acids in a fragment of another enzyme gives an enzyme with the same new and valuable characteristic. The formulation of claims 18-43 is so complicated because of all the different combinations of amino acid substitutions.

Thus they do not comply with Art. 6. PCT prescribing that claims shall be clear and concise.

2  
INTERNATIONAL SEARCH REPORT

International application No.  
PCT/DK 96/00057

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Dialog Information Services, file 155, MEDLINE. Dialog accession no. 08958150, MEDLINE accession no. 94273150, Nakatani H et al: "Effect of modifying histidine residues on the action of <i>Bacillus amylo-</i> <i>liquefaciens</i> and barley-malt alpha-amylases", & Carbohydr Res (NETHERLANDS) Apr 16 1994, 257 (1) p 155-61	1-17
Y	--	45-46
X	J. MED. BIOL., Volume 229, 1993, C. Chang et al, "Crystallization and Preliminary X-ray Crystallographic Analysis of alpha-Amylase from <i>Bacillus subtilis</i> " page 235 - page 238	1-17
	--	
A	WO 9100343 A2 (GIST-BROCADES N.V.), 10 January 1991 (10.01.91)	1-17
	--	
A	EP 0410498 A2 (GIST-BROCADES N.V.), 30 January 1991 (30.01.91)	1-17
	--	
A	JOURNAL OF BACTERIOLOGY, Volume 166, No 2, May 1986, G. L. Gray et al, "Structural Genes Encoding the Thermophilic alpha-Amylases of <i>Bacillus</i> <i>stearothermophilus</i> and <i>Bacillus licheniformis</i> " page 635 - page 643	1-17
	--	
P,X	WO 9535382 A2 (GISTBROCADES B.V.), 28 December 1995 (28.12.95), claims 1-2, abstract	45-46
	--	
Y	WO 9418314 A1 (GENENCOR INTERNATIONAL), 18 August 1994 (18.08.94)	45-46
	--	

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 96/00057

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>Chemical Abstracts, Volume 108, No 11, 14 March 1988 (14.03.88), (Columbus, Ohio, USA), Buisson, G. et al, "Three dimensional structure of porcine pancreatic alpha-amylase at 2.9 Å resolution. Role of calcium in structure and activity", page 325, THE ABSTRACT No 90927h, EMBO J. 1987, 6 (13), 3909-3916</p> <p>--</p>	45-46
Y	<p>Chemical Abstracts, Volume 112, No 15, 9 April 1990 (09.04.90), (Columbus, Ohio, USA), Vihinen, Mauno et al, "Site-directed mutagenesis of a thermostable alpha-amylase from Bacillus stearothermophilus: putative role of three conserved residues", page 347, THE ABSTRACT No 135178r, J. Biochem 1990, 107 (2), 267-272</p> <p>--</p>	45-46
A	<p>US 4600693 A (KAREN L. KINDLE ET AL), 15 July 1986 (15.07.86)</p> <p>--</p>	45-46
A	<p>Chemical Abstracts, Volume 112, No 19, 7 May 1990 (07.05.90), (Columbus, Ohio, USA), Holm, Liisa et al, "Random mutagenesis used to probe the structure and function of Bacillus stearothermophilus alpha-amylase", page 351, THE ABSTRACT No 174785f, Protein Eng. 1990, 3 (3), 181-191</p> <p>1 -- -----</p>	45-46

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK96/00057

## Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2. ☒ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:  
  
see next sheet
  
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see next sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:  
Claims 1-17 directed to a method of constructing alpha-amylase variants  
and claims 45-46 directed to an alpha-amylase.
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☒ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1992)

INTERNATIONAL SEARCH REPORT  
Information on patent family members

01/04/96

International application No.

PCT/DK 96/00057

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A2- 9100343	10/01/91	AU-B,B- 629959 AU-A- 5939790 CA-A- 2032518 EP-A,A,A 0409299 JP-T- 4500609	15/10/92 17/01/91 30/12/90 23/01/91 06/02/92
EP-A2- 0410498	30/01/91	AU-B- 638263 AU-A- 5953890 CA-A- 2030554 CN-A- 1050220 JP-T- 4500756 US-A- 5364782 WO-A,A,A 9100353	24/06/93 17/01/91 30/12/90 27/03/91 13/02/92 15/11/94 10/01/91
WO-A2- 9535382	28/12/95	NONE	
WO-A1- 9418314	18/08/94	NONE	
US-A- 4600693	15/07/86	NONE	